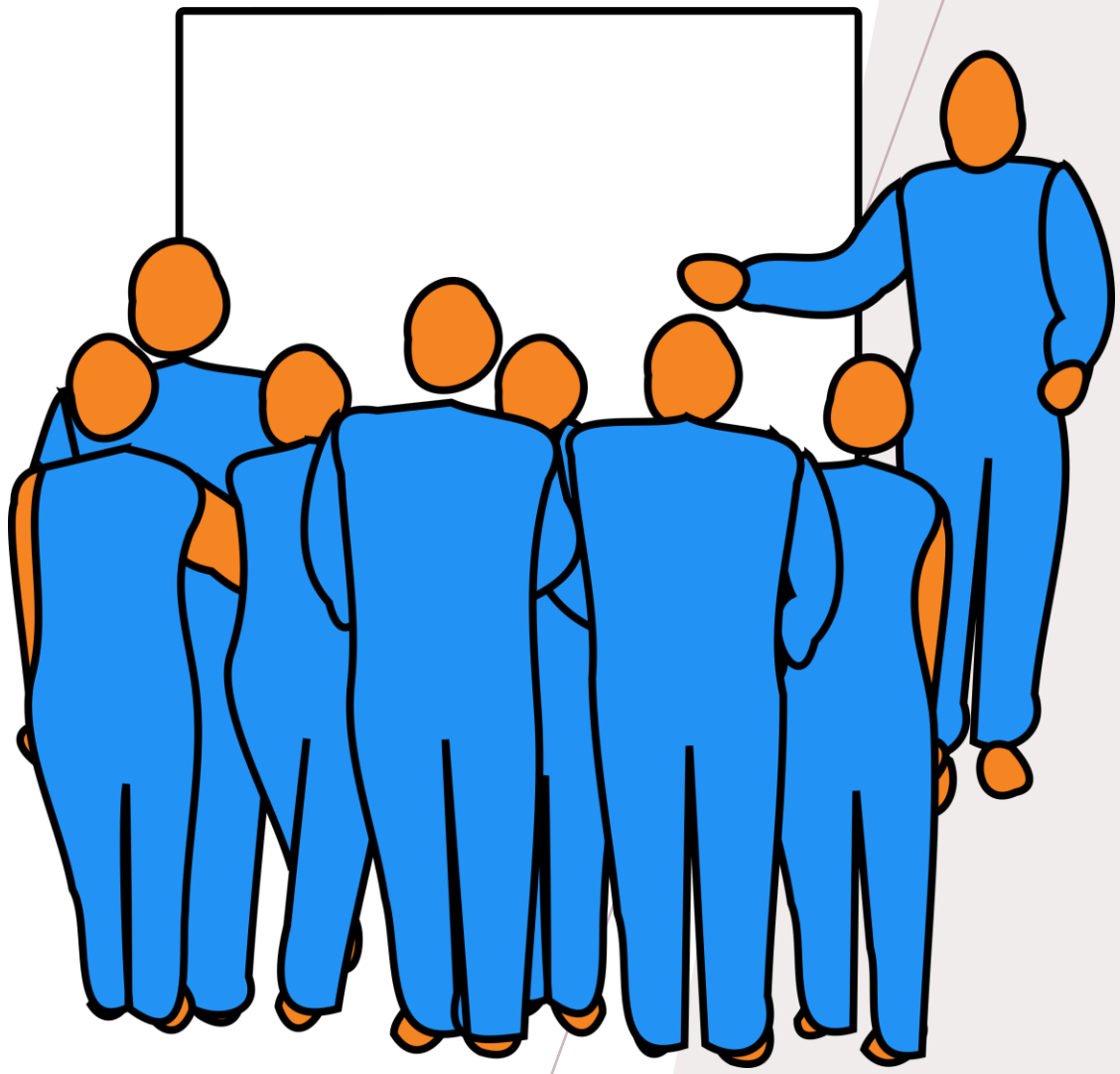

# JOURNAL CLUB

07 November 2025

Presenter

Paballo Adelina Khotso

Msc. Medical Epidemiology

*Original Article*

MDM
Medical Decision Making

*Medical Decision Making*
2021, Vol. 41(2) 194–208
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# Joining the Dots: Linking Disconnected Networks of Evidence Using Dose-Response Model-Based Network Meta-Analysis

**Hugo Pedder, Sofia Dias, Meg Bennetts, Martin Boucher, and Nicky J. Welton**

Introduction

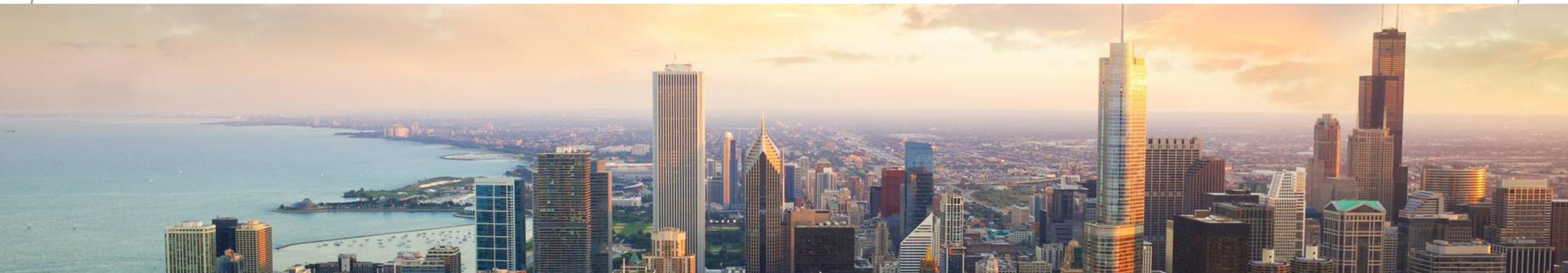
Methods

Results

Discussion

Conclusion

# *INTRODUCTION*

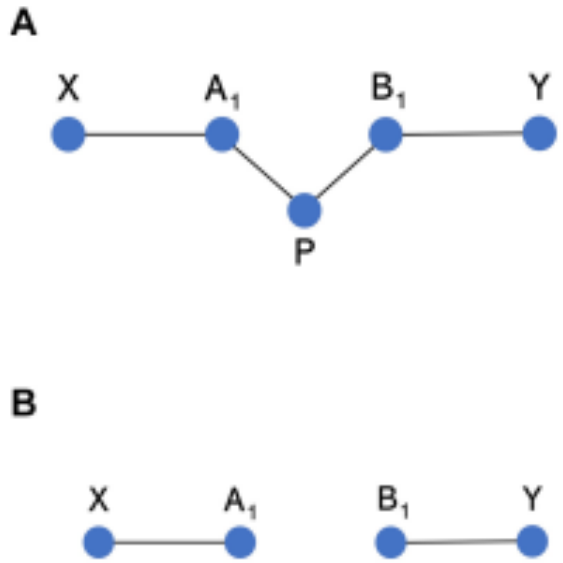


# *BACKGROUND*

- Health care policy decisions use cost effectiveness analysis to support decision making of health professionals
- Estimating the relative effectiveness of multiple treatments options is an important element.
- Typically done by network meta-analysis

# *NETWORK META-ANALYSIS (NMA)*

- Method of pooling the results of primary studies to enable a comparison of multiple treatments options simultaneously.
- Provided that they form a connected network of treatment comparisons.

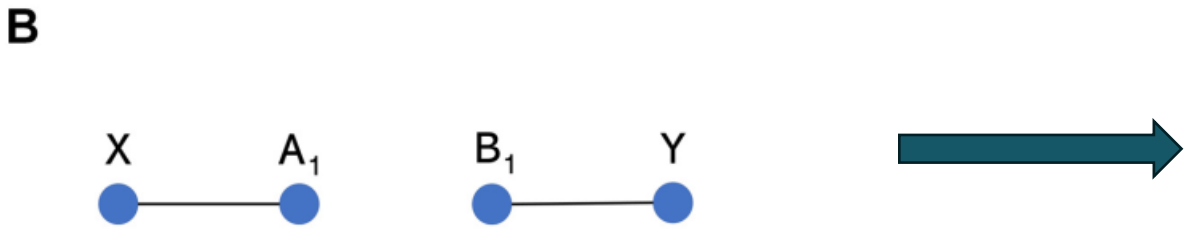


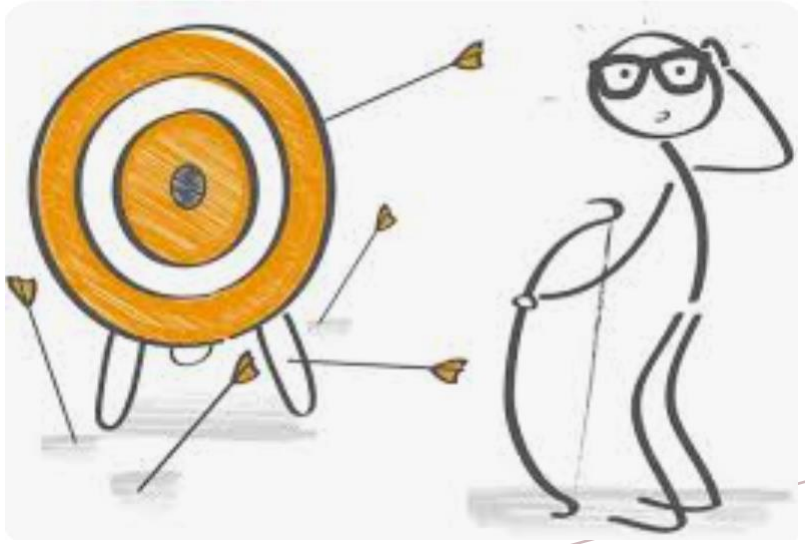

A. Connected Network

B. Disconnected Network

# *DISCONNECTED NETWORKS IN NMA*

- Make it impossible to obtain relative effect estimates of disconnected treatment comparisons
- Or  lead to estimation of very imprecise relative effects.



# *HOW TO DEAL WITH DISCONNECTED NETWORKS IN NMA*

METHODS

# *METHODS*

1. Use of observational or registry data
2. Evidence in other populations
3. Expert opinion
4. Population adjustment methods
5. Hierarchical models
6. Modeling intervention components

# *EXAMPLES*

1. **Using Evidence in other populations**

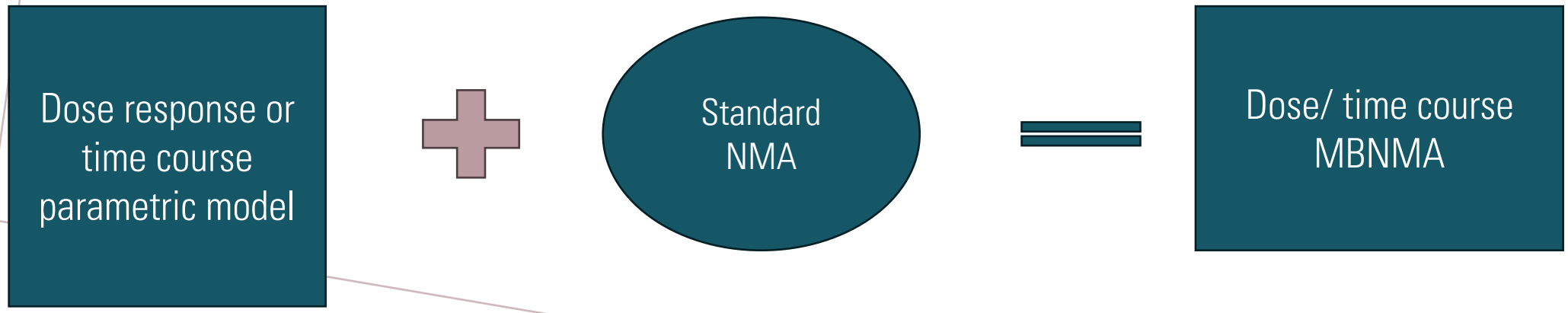
- In a study comparing treatments for plaque psoriasis in **children and young people.**
- Adalimumab was disconnected from the network
- Evidence from an adult trial was used to connect the NMA comparing the treatments of interest.

2. **Using observational data and population adjustment methods.**

- Study for relapsed and refractory multiple myeloma
- There was no RCT evidence connecting pomalidomide with comparators panobinostat or bendamustine.
- Analysis of individual patient data from single arms and population adjustment methods were used to connect the network.
- However, **all these methods make strong and typically untestable assumptions**

# MODEL-BASED NETWORK META-ANALYSIS (MBNMA)

- **New methodology** that has the potential to connect networks
- By using evidence on
- Multiple doses of 1 or more agents **(dose response)**
- Observations at multiple follow-up times **(time course)**
- And still preserves randomization of included RCTs

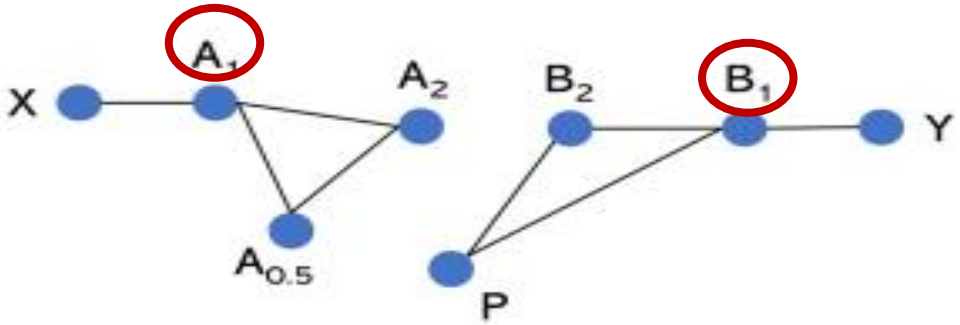


# ILLUSTRATION

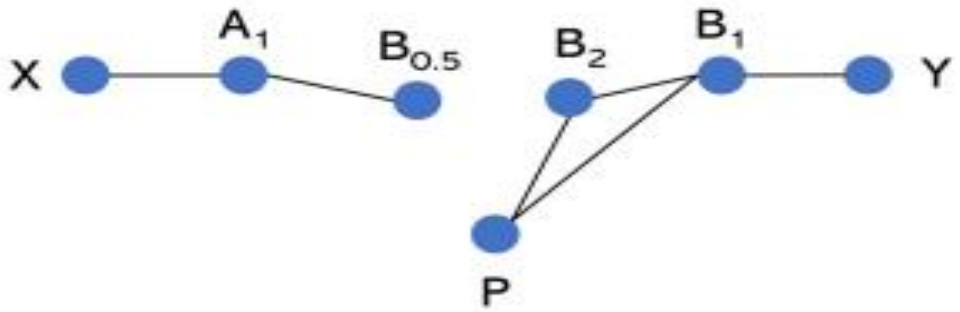
Studies of A

Studies of B

C




D

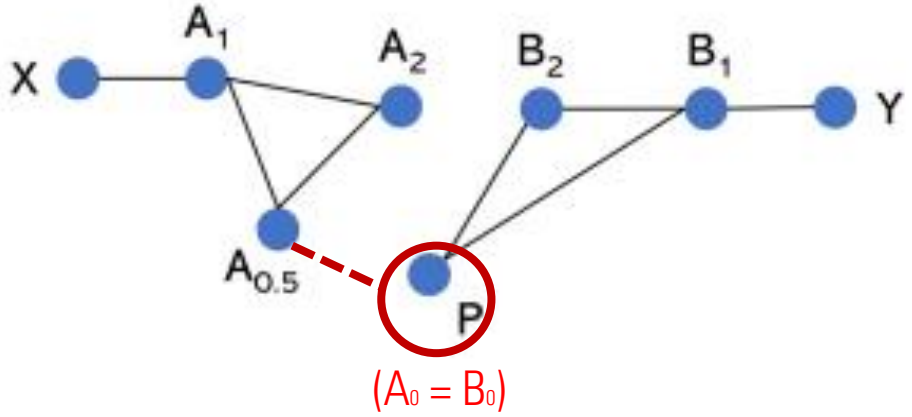



- $A_1$ and $B_1$ are disconnected.
- In figure C, A and B are disconnected due to **absence of common comparator**.
- In figure D, A and B are disconnected due to **comparison with unlicensed dose ($B_{0.5}$)**

**Treatments** are defined by agent, (A, B, X, Y)
Dose **1** = **licensed dose**
**Dose 0.5 = ½ of licensed dose**

# APPLYING MBNMA

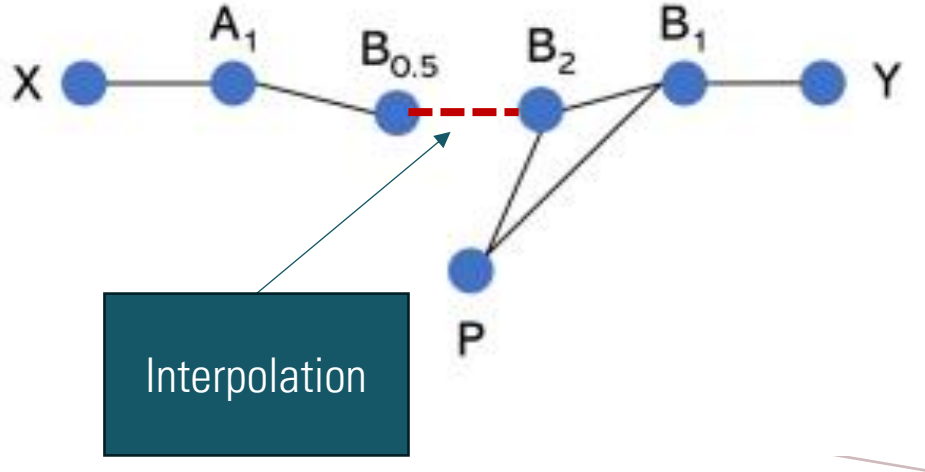
**C**




1. Use MBNMA modeling to connect the network by estimating A placebo response of agents.

Placebo response (p) = Dose 0 of each agent ($A_0 = B_0$)

**D**




2. Connects the different dose of treatment B (e.g $B_{0.5}$ ) to other doses of B by interpolation.

# *AIM OF STUDY*

- To illustrate the potential of dose-response MBNMA to connect and strengthen evidence networks in a range of different scenarios.

1. Describe the MBNMA method

2. Introduce a network of triptans for migraine relief (data set)

3. Manipulate the data set to obtain a set of scenario networks with different features to illustrate the performance of the MBNMA method

4. Present and compare results from MBNMA and NMA in each scenario.

# METHODS

# 1. THE STANDARD NMA METHOD

- **Study-specific relative treatment effect** ($\delta_{i,k}$) is assumed to follow a **normal distribution** around the **average (mean) treatment effect** for that comparison.
- This **mean treatment effect** reflects the **difference between the treatment ($t_{i,k}$)** used in arm *k* and the **reference treatment ($t_{i,1}$)** used in control arm (1) of each study.
- The **between-study variance ($\tau^2$)** represents how much treatment effects vary across studies.

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

Mean treatment effect ($t_{i,k}$) vs the network reference treatment

# 2. THE DOSE-RESPONSE MBNMA METHOD

- The dose-response MBNMA model extends the standard NMA model by incorporating a **dose-response relationship.**
- It defines the treatment in arm *k* of study *i* as a **specific dose ($x_{i,k}$)** of a **specific agent ($a_{i,k}$)**.

$$\delta_{i,k} \sim N(f(x_{i,k}, a_{i,k}) - f(x_{i,1}, a_{i,1}), \tau^2)$$

**Dose-response function** for **specific dose ($x_{i,k}$)** of a **specific agent ($a_{i,k}$)**. In arm *K*

**Dose-response function** for **specific dose ($x_{i,k}$)** of a **specific agent ($a_{i,k}$)**. In control arm of study *i*

# *DOSE-RESPONSE FUNCTION*

- Depends on the number of doses of an agent included in RCTs in the network.

## 1. Exponential model function

- In this model, a **single** dose-response **parameter** is estimated for each agent.
- Studies with >2 doses (one of which could be placebo) of each agent are required to estimate **rate parameter** (i.e How fast the effect increase or decrease with dose)

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

The rate parameter agent in arm (*k*) of study *i*

Exponential term

# DOSE-RESPONSE FUNCTION

## 2. Emax function

- Studies with at least 3 doses of a specific agent are required.
- In this model, **2** dose-response **parameters (**Emax and ED50 )are estimated for each agent.
- The Emax and ED50 parameters may be correlated.
- This correlation estimated by specifying a bivariate normal distribution with a Wishart prior on the covariance matrix.

Maximum achievable effect of specific agent

$$f(x_{i,k}, a_{i,k}) = E_{0,i} + \frac{E_{\max, a_{i,k}} x_{i,k}}{ED_{50, a_{i,k}} + x_{i,k}}$$

Half-maximal effective dose

# *IMPLEMENTATION*

- Multiple datasets were created according to scenario.
- Each data set was analyzed where possible using **standard NMA** and **dose-response MBNMA.**
- **Common (Fixed)** and **random effects** models were compared for each model (NMA and MBNMA).
- Relative efficacy was presented in **posterior medians** and **95% credible intervals** (95% CrIs).
- e.g MBNMA with common effect vs MBNMA with random effect

# *IMPLEMENTATION*

- **Model selection strategy**

1. Deviance information criterion (**DIC**) (defined as sum of the effective number of parameters added to the residual deviance) was used to **compare models**

- **Lowest DIC = Best model**
- Models with DIC within 3 points of **Best model** were identified, of these models, the simplest was preferred.

| NMA or MBNMA Models with : | Preferred models (simplest model) |
|---|---|
| Fixed effect **or** Random effect | Fixed effect |
| Exponential dose-response **or** Emax dose-response function | exponential dose-response |

- MBNMAdose version 0.2.727 package in R version 3.6.1 was used

# *INTRODUCING THE DATASET*

Meta-Analysis > Cephalalgia. 2014 Apr;34(4):258-67. doi: 10.1177/0333102413508661. Epub 2013 Oct 9.

**Comparative efficacy of triptans for the abortive treatment of migraine: a multiple treatment comparison meta-analysis**

Kristian Thorlund [1], Edward J Mills, Ping Wu, Elodie Ramos, Anjan Chatterjee, Eric Druyts, Peter J Goadsby

- A data set of published RCTs for the efficacy of triptans in migraine relief.
- 70 studies
- 22 treatments
- 7 agents + placebo
- Doses are standardized to multiples of each agent's **"common"** dose.

# *DATASET MANIPULATION*

- From the complete data set, manipulated data sets were generated by removing **specific treatments** and **studies** to represent **several scenarios** that might be **found in practice.**
- Then performance of NMA and MBNMA methods in each scenario were compared.
- If only a **single arm remained** in a study after excluding another treatment arm, that study was excluded in the analysis.

# *SCENARIOS*

1. DATA SET MANIPULATION
2. RESULTS FOR THAT SCENARIO

# *SCENARIO 1*

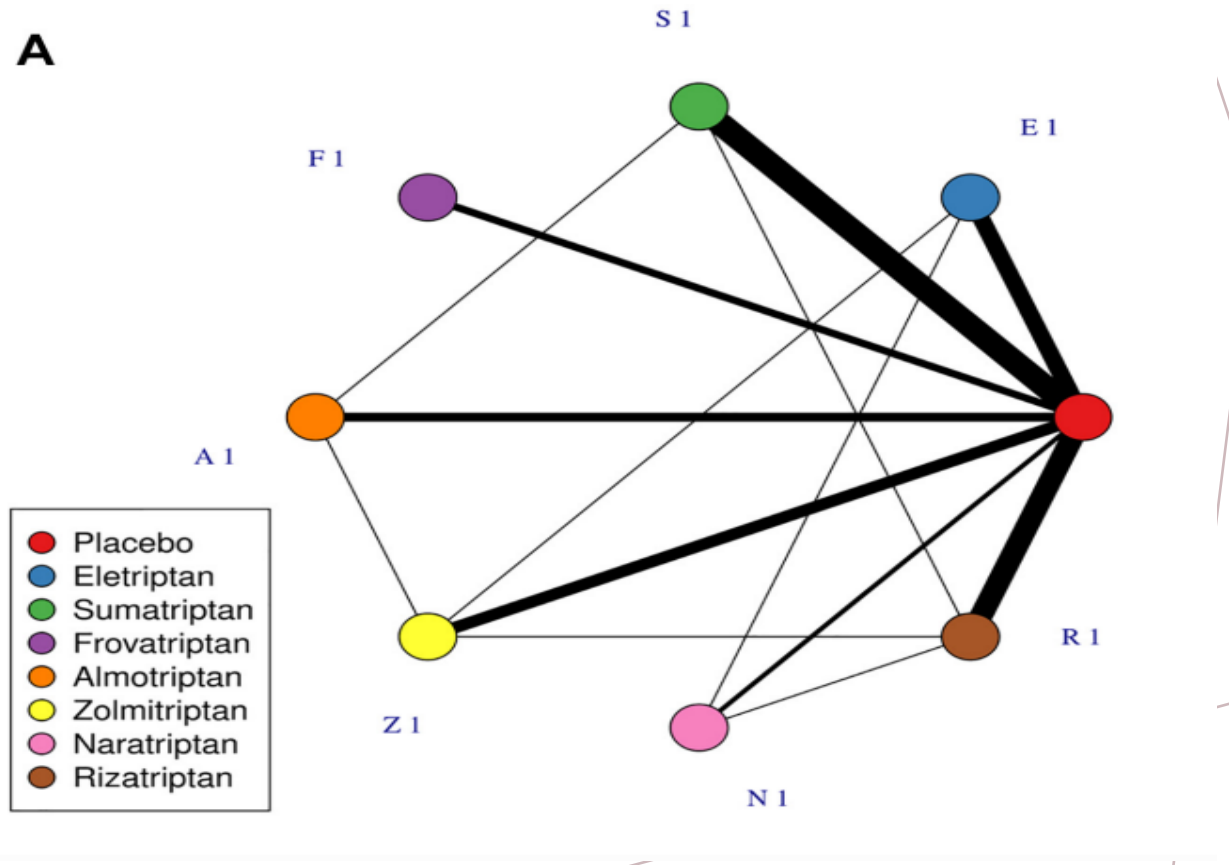
## Connected networks

# SCENARIO 1A

common

- The network is **connected** using c**ommon** (licensed) dose per agent.
- This scenario is similar to data sets found in most studies, **whereby only licensed doses of each agent are of interest.**

- **Manipulated data set included 59 RCTs**
- Only a **single common dose** of each treatment and placebo is included.
- 7 treatments + placebo



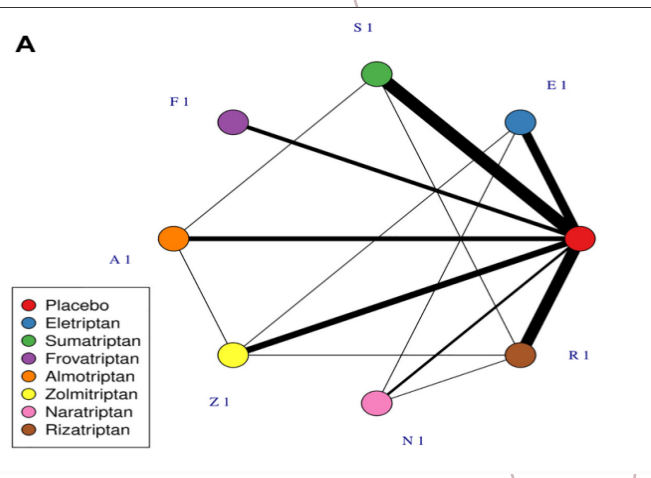
# SCENARIO 1A RESULTS

- Model fit

**Table 1** Model Fit Statistics for All Models Investigated in Scenario 1A and 1B Data Sets

| Data Set | No. of Data Points | Residual Deviance | DIC[a] | pD[b] | Model | Dose-Response Function | Treatment Effects | Between-Study SD (95% CrI) |
|---|---|---|---|---|---|---|---|---|
| Scenario 1A | 122 | 202.3 | 66.6 | 268.9 | NMA | NA | Common | NA |
| Scenario 1A | 122 | 124.0 | 96.3 | 220.3 | NMA | NA | Random | 0.36 (0.25, 0.50) |
| Scenario 1A | 122 | 201.7 | 66.1 | 267.8 | MBNMA | Exponential | Common | NA |
| Scenario 1A | 122 | 124.0 | 96.2 | 220.2 | MBNMA | Exponential | Random | 0.36 (0.25, 0.50) |
| Scenario 1A | 122 | NC | NC | NC | MBNMA | Emax | Common | NA |
| Scenario 1A | 122 | NC | NC | NC | MBNMA | Emax | Random | NC |
| Scenario 1B | 182 | 269.0 | 93.3 | 362.3 | NMA | NA | Common | NA |
| Scenario 1B | 182 | 190.6 | 131.6 | 322.2 | NMA | NA | Random | 0.27 (0.18, 0.37) |
| Scenario 1B | 182 | 296.5 | 77.1 | 373.6 | MBNMA | Exponential | Common | NA |
| Scenario 1B | 182 | 189.4 | 125.1 | 314.5 | MBNMA | Exponential | Random | 0.28 (0.20, 0.37) |
| Scenario 1B | 182 | 266.8 | 80.9 | 347.7 | MBNMA | Emax | Common | NA |
| Scenario 1B | 182 | 191.7 | 121.6 | 121.6 | MBNMA | Emax | Random | 0.24 (0.16, 0.34) |

[a]DIC: deviance information criterion = pD + residual deviance.
[b]pD: The effective number of parameters calculated using the Kullback-Leibler divergence[30] for model-based network meta-analysis (MBNMA) and the plugin method[29] for NMA.
NC, Markov chain Monte Carlo chains did not converge; model was not identifiable.
NA: not applicable

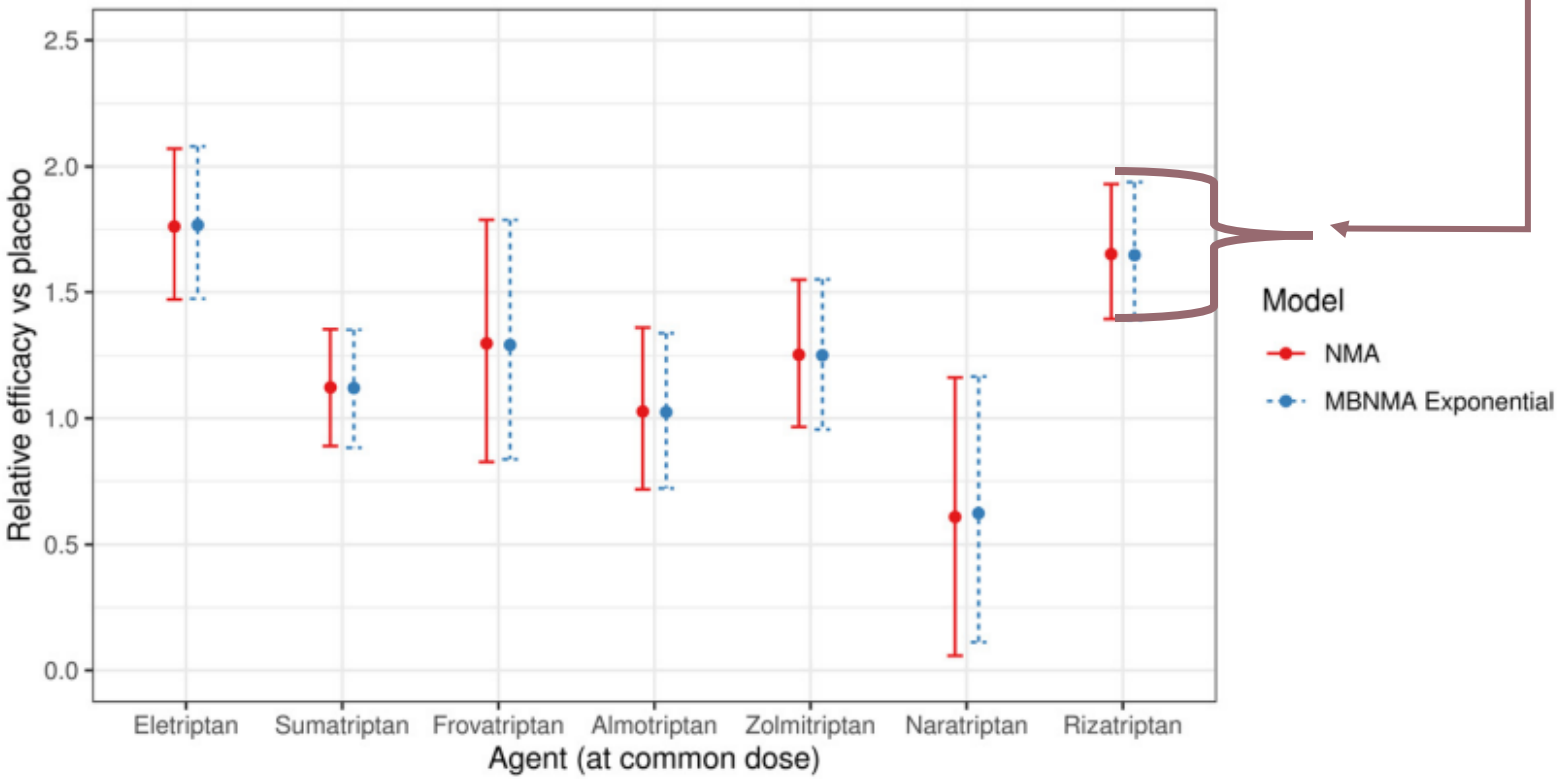


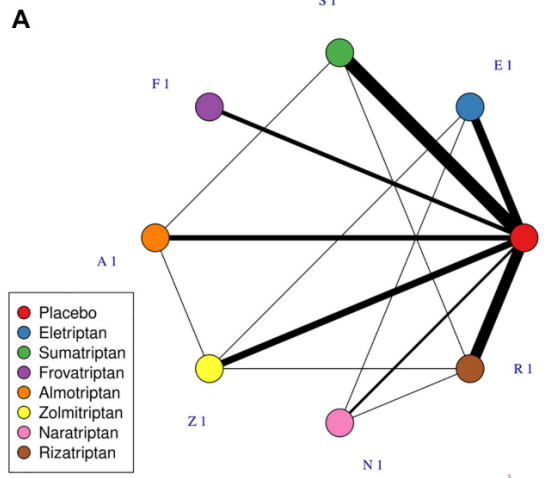

- The exponential MBNMA model and NMA with random effect was chosen.
- Model performance of NMA (DIC=**96.3**) and MBNMA (DIC= **96.2**) is **similar.**

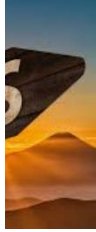
# SCENARIO 1A RESULTS

- Relative effect

Relative effects from selected NMA and MBNMA models **were very similar.**



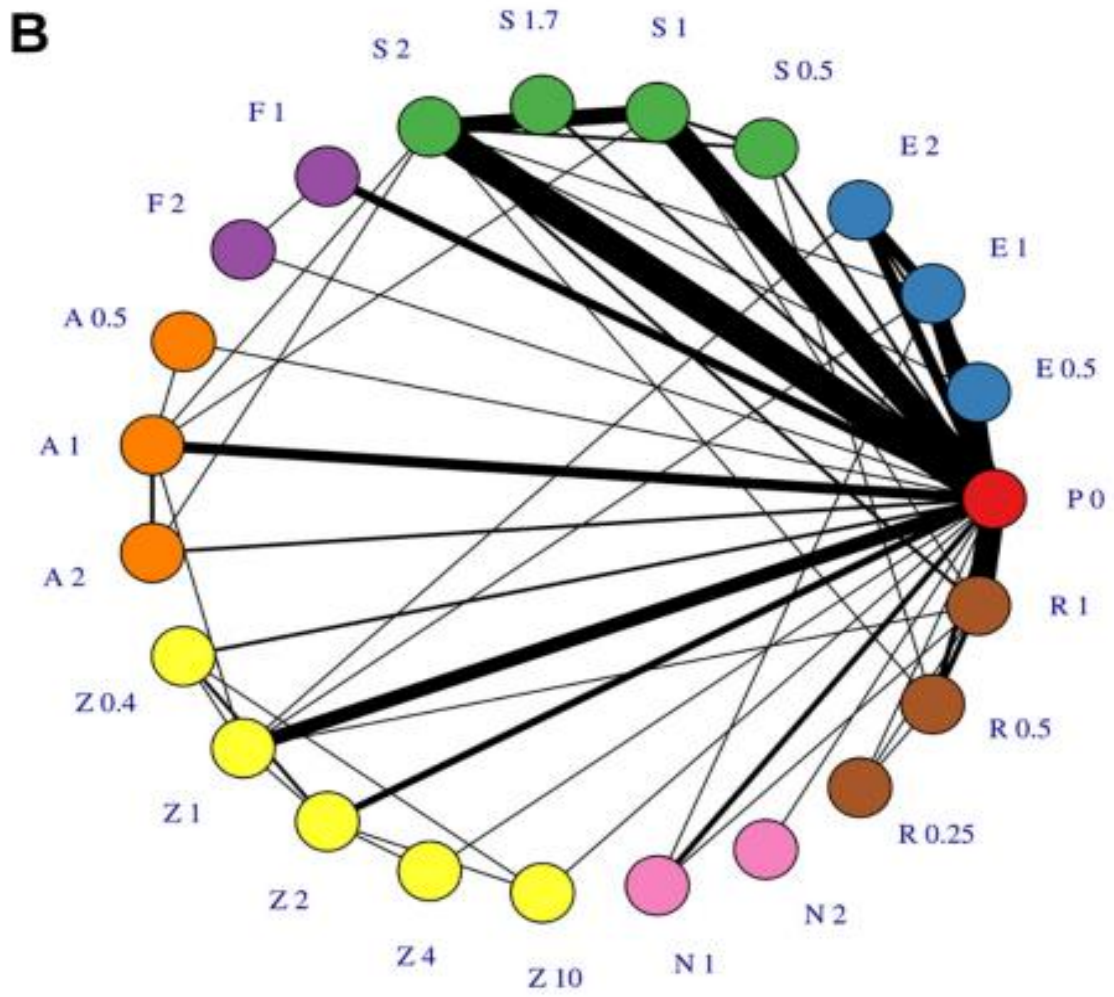



Because of the **lack of dose response information**,

**There was no gain in precision** of the estimates in the MBNMA model vs the NMA model.

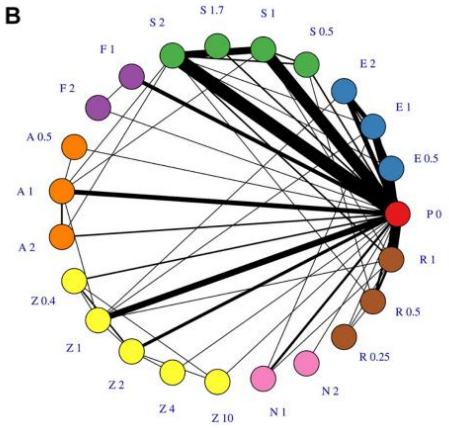
# SCENARIO 1B

- Dataset was generated in such a way that a network was **connected** using evidence of **all available doses of each agen**t and placebo.
- 70 studies,
- 22 treatments, 7 agents, and a placebo

# SCENARIO 1B RESULTS

- Model fit

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[b]pD: The effective number of parameters calculated using the Kullback-Leibler divergence[30] for model-based network meta-analysis (MBNMA) and the plugin method[29] for NMA.
NC, Markov chain Monte Carlo chains did not converge; model was not identifiable.

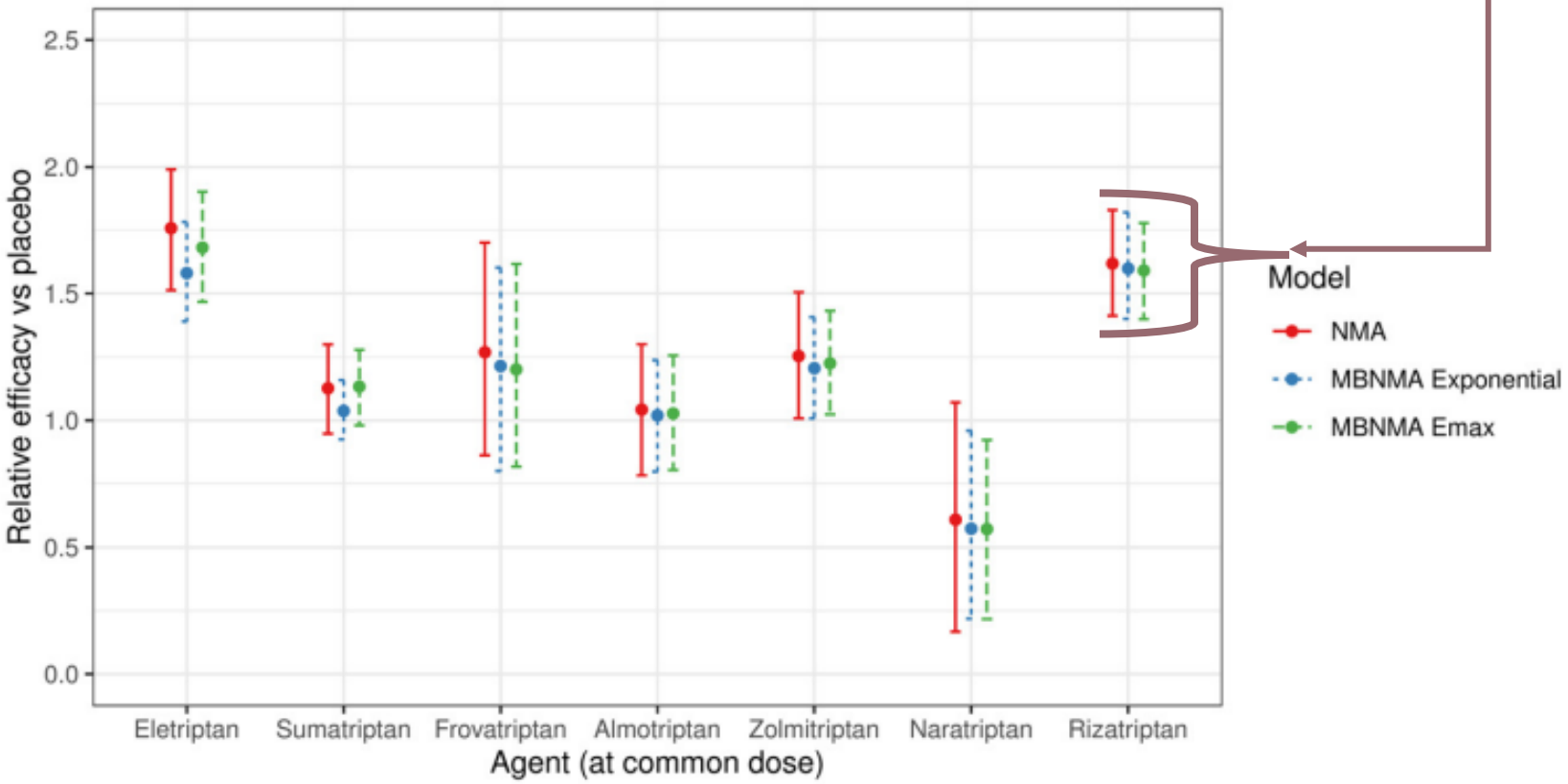
NA: not applicable

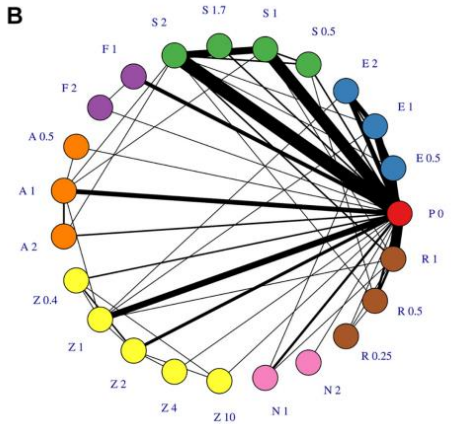
- Random effects models were selected for the NMA and MBNMA.
- An Emax dose response function was selected for the MBNMA model (DIC =121.6)

# *SCENARIO 1B RESULTS*

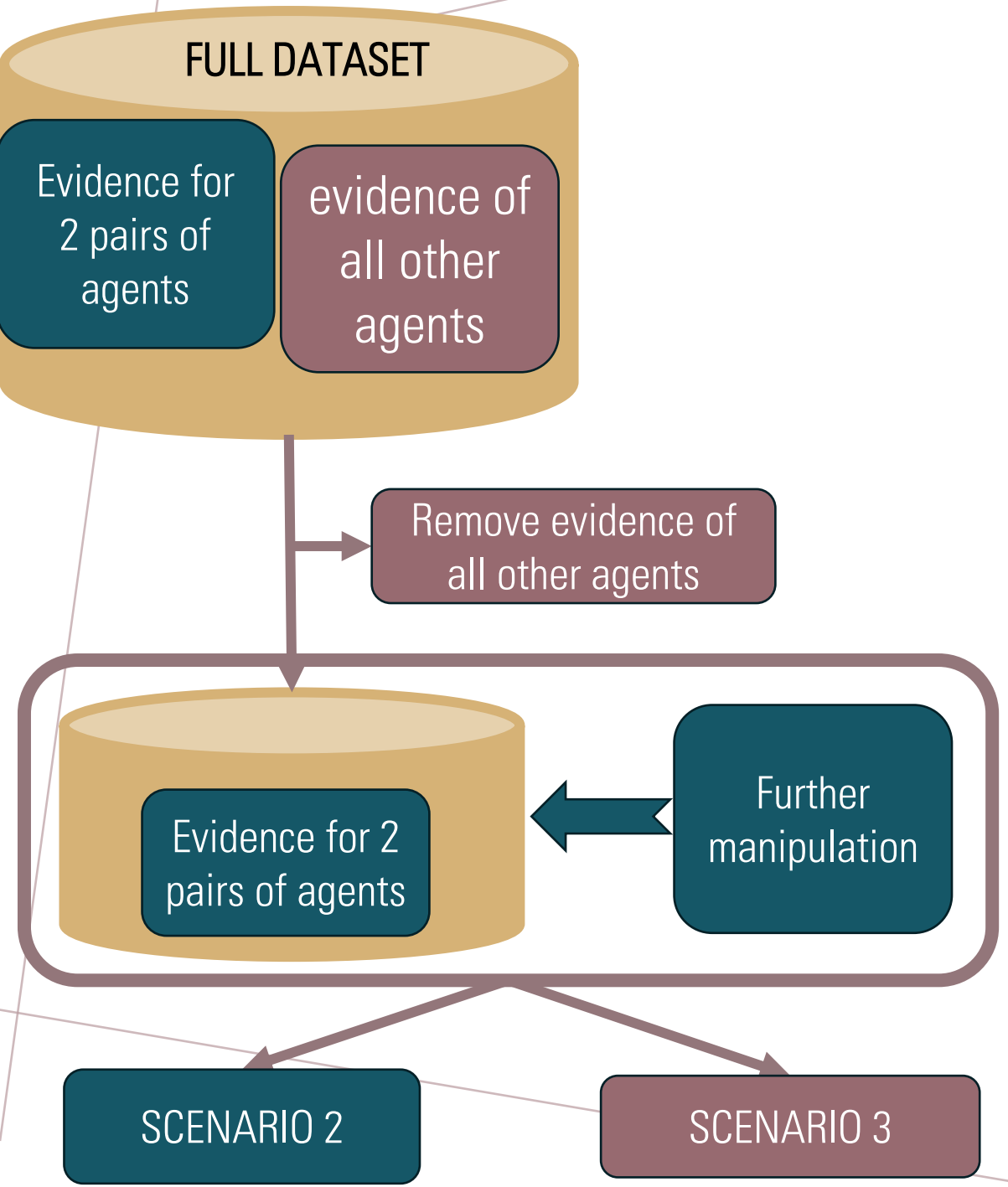
**MBNMA estimates** were **more precise** than NMA estimates

- **Relative effect**




- **Additional information** gained from modeling the dose-response relationship led to **increased precision** in MBNMA estimates vs NMA estimates.




# SCENARIO 2 AND 3

- Disconnected networks
- The objective was to compare 2 treatments of interest (agents of interest at the common dose)
- The datasets were manipulated to obtain **disconnected networks for scenarios.**

# *SCENARIO 2 AND 3*

**Step 1**

- Fit the MBNMA models to disconnected networks using method described in previous study
- Calculate relative effects

**Step 2**

- Add data to create “augmented datasets” to connect the network
- Calculate relative effects

**Step 3**

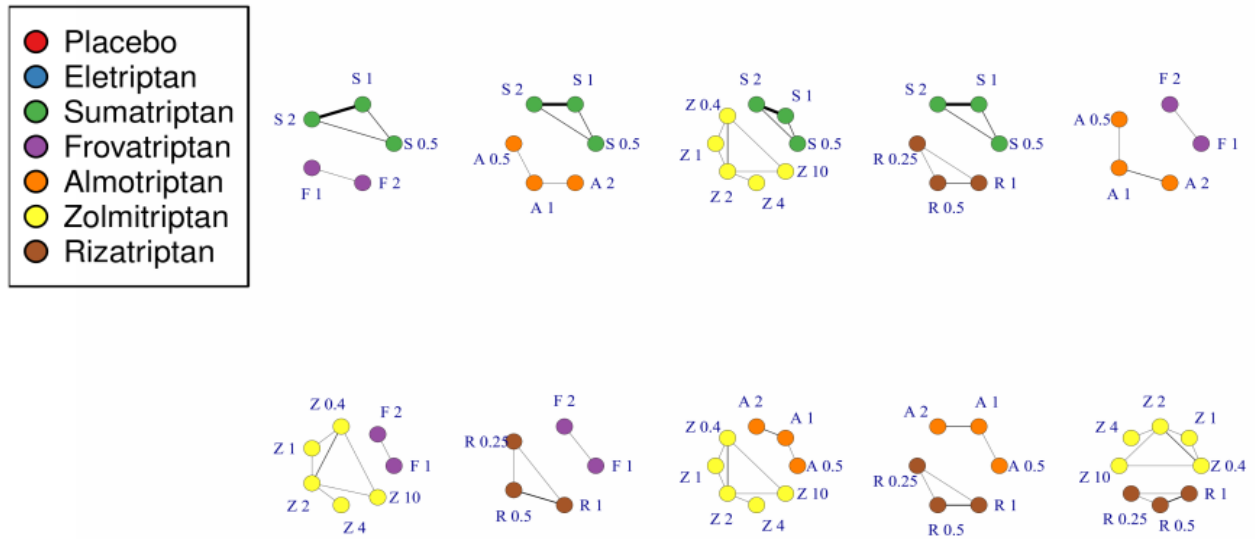
- Compare the relative effects estimated between 2 datasets and assess level of agreement

# SCENARIO 2

- Created situation whereby the network is **disconnected** due to absence of common comparator (e.g placebo).
- There is **evidence on different doses for an agent** of interest but there is no common comparator.
- **All placebo arms** for each pair of agents comparison were removed

Evidence about different doses for each pair of agent of interest

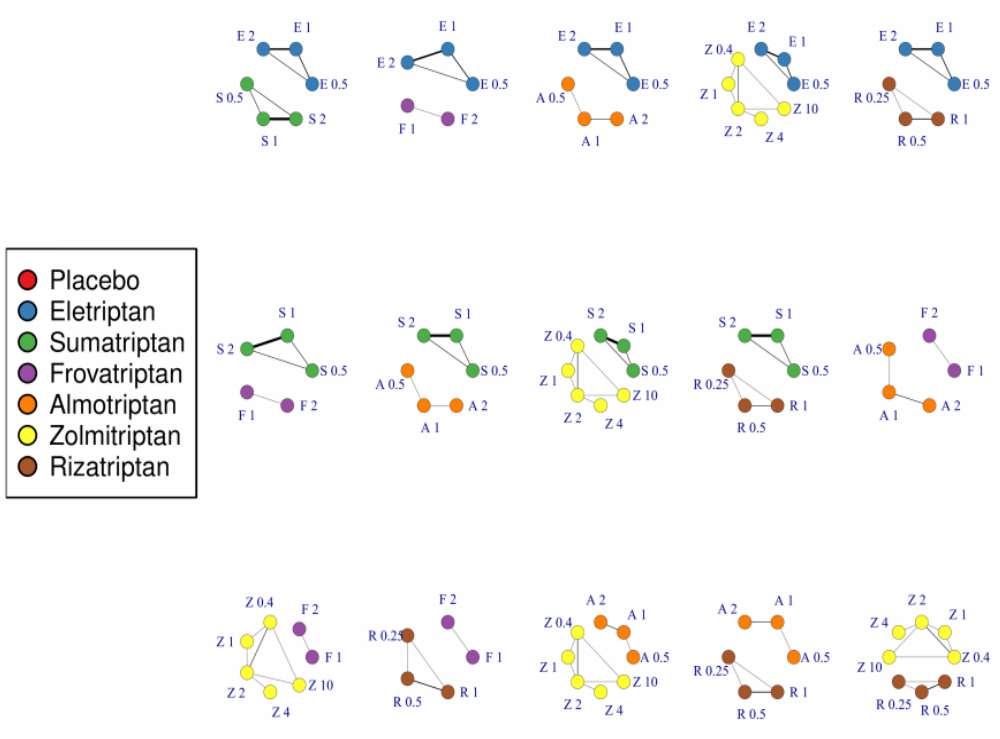
Remove placebo arm



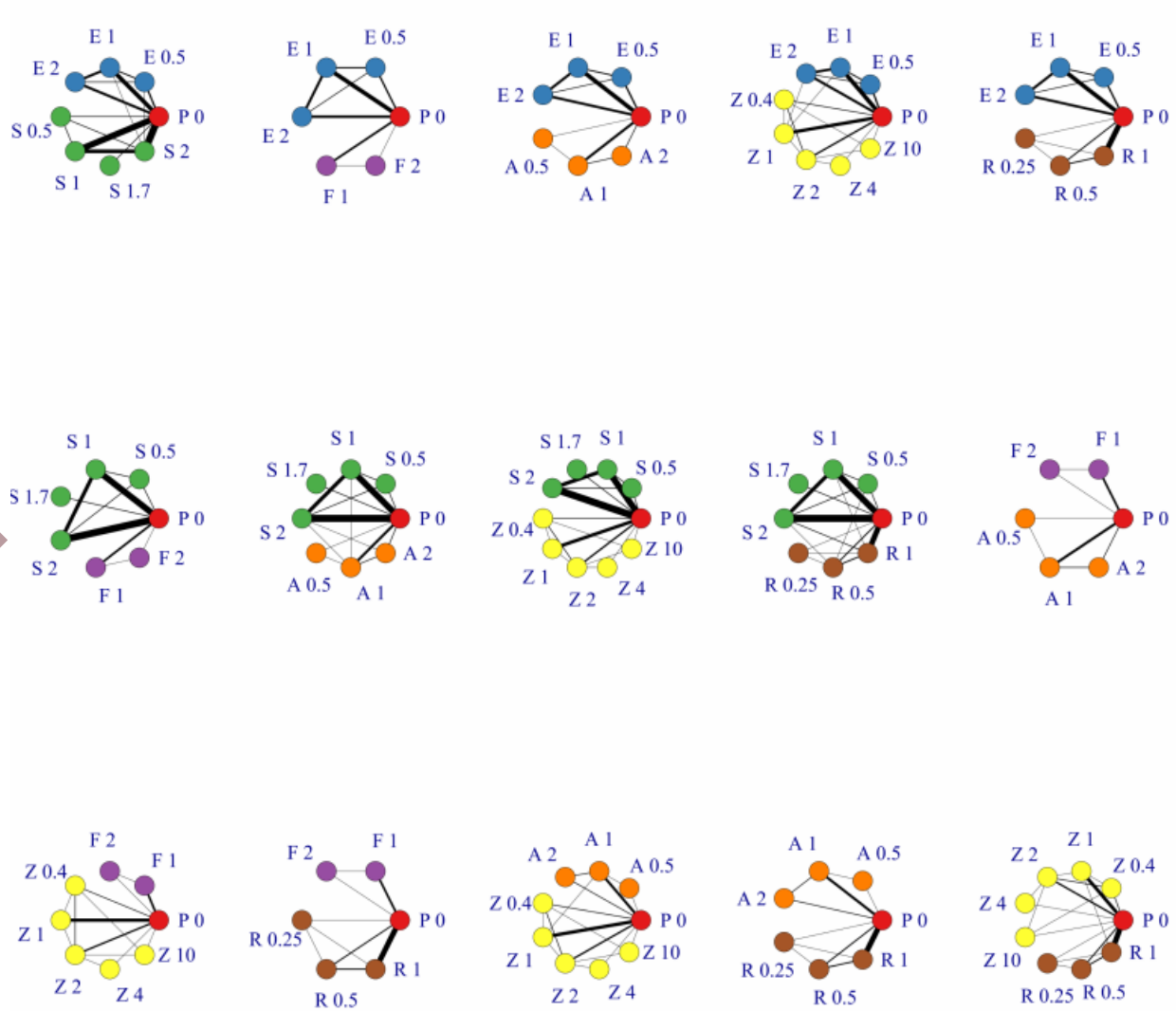
# SCENARIO 2

- Generation of augmented datasets
- BY including comparisons between **any doses** of the included agents **versus placebo**

## Disconnected networks




## Connected networks by augmentation



# *SCENARIO 2 RESULTS*


- NMA models could not be estimated because of the networks being disconnected.
- In all **disconnected data sets**,

an exponential dose response MBNMA was selected with common treatment effects

- In **Augmented data sets**,
- For **MBNMA** models, **an Emax dose-response** function was selected for **12 of 15** data sets.
- **Random treatment effects** were selected over common effects **in 12 of 15** data sets for both NMA and MBNMA models.

# SCENARIO 2 RESULTS

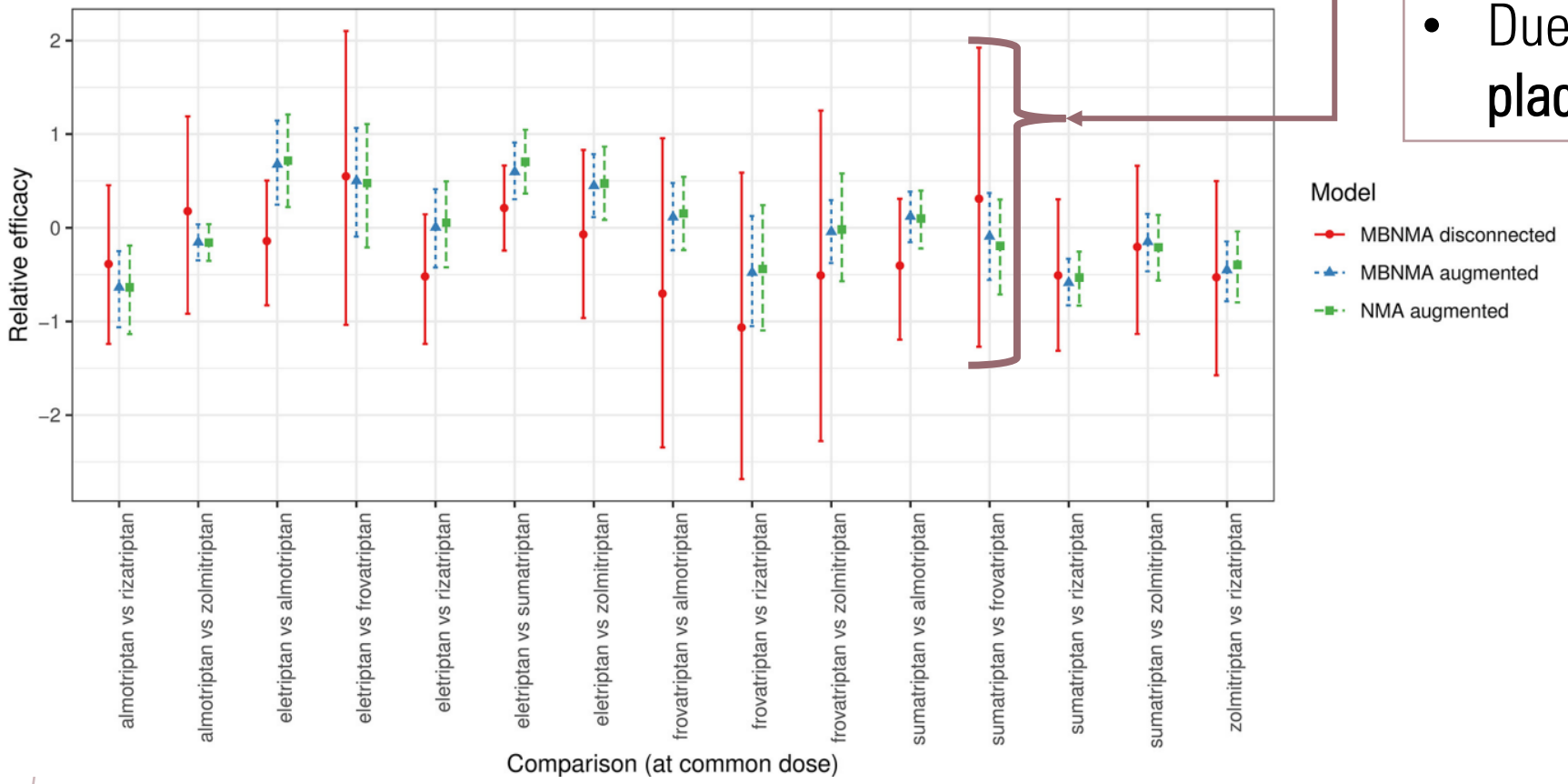

**Table 2** Model Fit Statistics for Selected Models in Each Data Set Analyzed in Scenario 2

| Data Set Number | Data Set | Agent 1 | Agent 2 | No. of Data Points | Residual Deviance | DIC[a] | pD[b] | Model | Dose-Response Function | Treatment Effects | Between-Study SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Initial | Almotriptan | Rizatriptan | 13 | 12.0 | 20.0 | 8.0 | MBNMA | Exponential | Common | NA |
| 1 | Augmented | Almotriptan | Rizatriptan | 45 | 48.9 | 81.5 | 32.6 | MBNMA | Exponential | Random | 0.27 (0.09−0.5) |
| 1 | Augmented | Almotriptan | Rizatriptan | 45 | 48.1 | 83.3 | 35.3 | NMA | NA | Random | 0.32 (0.12−0.59) |
| 2 | Initial | Almotriptan | Zolmitriptan | 14 | 11.0 | 19.2 | 8.2 | MBNMA | Exponential | Common | NA |
| 2 | Augmented | Almotriptan | Zolmitriptan | 44 | 42.1 | 63.0 | 21.0 | MBNMA | Emax | Common | NA |
| 2 | Augmented | Almotriptan | Zolmitriptan | 44 | 45.3 | 71.6 | 26.3 | NMA | NA | Common | NA |
| 3 | Initial | Eletriptan | Almotriptan | 22 | 24.0 | 36.3 | 12.3 | MBNMA | Exponential | Common | NA |
| 3 | Augmented | Eletriptan | Almotriptan | 46 | 48.1 | 81.7 | 33.6 | MBNMA | Emax | Random | 0.3 (0.14−0.5) |
| 3 | Augmented | Eletriptan | Almotriptan | 46 | 48.3 | 84.5 | 36.3 | NMA | NA | Random | 0.34 (0.16−0.58) |
| 4 | Initial | Eletriptan | Frovatriptan | 18 | 21.6 | 31.9 | 10.2 | MBNMA | Exponential | Common | NA |
| 4 | Augmented | Eletriptan | Frovatriptan | 42 | 42.1 | 76.0 | 34.0 | MBNMA | Emax | Random | 0.4 (0.23−0.67) |
| 4 | Augmented | Eletriptan | Frovatriptan | 42 | 42.8 | 77.0 | 34.2 | NMA | NA | Random | 0.43 (0.23−0.71) |
| 5 | Initial | Eletriptan | Rizatriptan | 23 | 27.9 | 39.9 | 12.1 | MBNMA | Exponential | Common | NA |
| 5 | Augmented | Eletriptan | Rizatriptan | 61 | 63.1 | 110.2 | 47.2 | MBNMA | Emax | Random | 0.38 (0.23−0.57) |
| 5 | Augmented | Eletriptan | Rizatriptan | 61 | 63.9 | 112.0 | 48.1 | NMA | NA | Random | 0.4 (0.24−0.63) |

- In all **disconnected** (initial) data sets, an exponential dose response MBNMA was selected with common treatment effects.

# SCENARIO 2 RESULTS

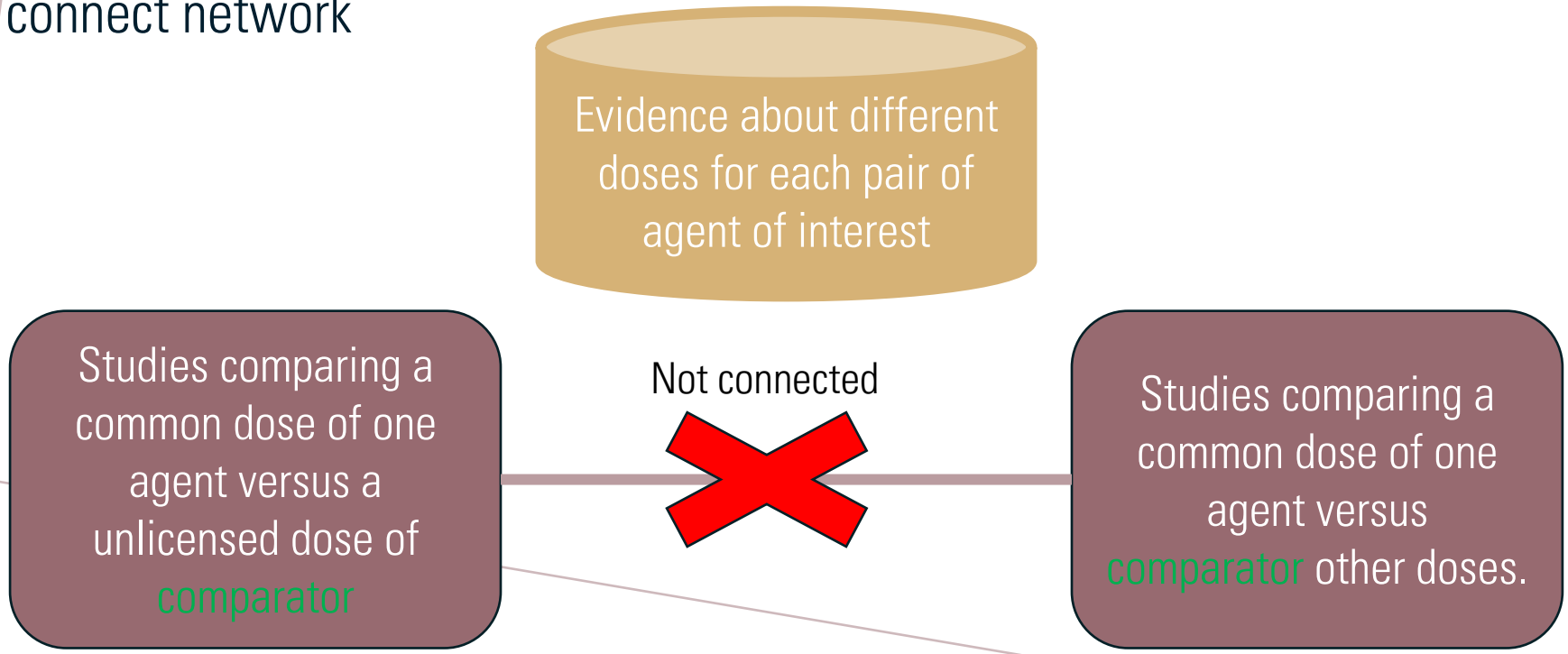
- **High uncertainty** in relative effects from disconnected MBNMA models
- Due to **sparse data** and **lack of placebo evidence** at lower doses




- **Augmenting data** with placebo arms improved network connectivity
- **MBNMA and NMA estimates** became very similar after augmentation.
- **MBNMA showed slightly higher precision** with **narrower 95% CrIs**

# SCENARIO 3

- Created situation whereby the network is **disconnected** due to comparison with a dose that has not been evaluated in other trials.
- There is **evidence on** the treatment of interest been investigated in studies only comparing it with unlicensed dose of a comparator.
- The augmented data sets that include comparisons between all doses of both agents were generated to connect network



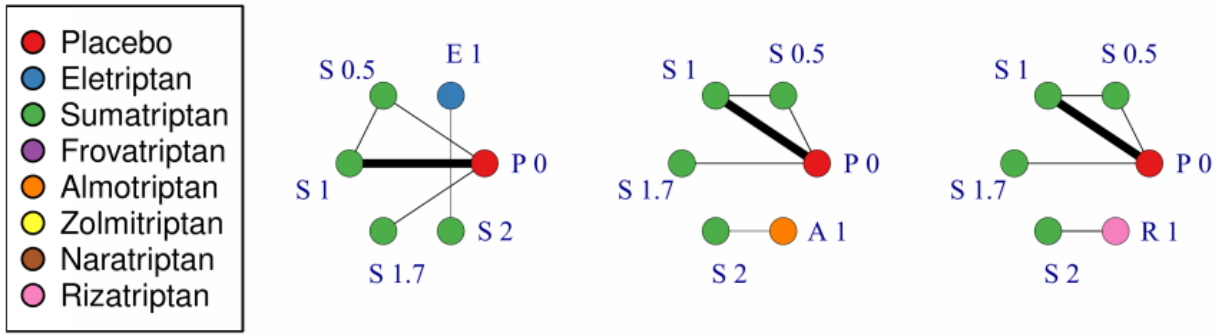
# SCENARIO 3

Evidence about different doses for each pair of agent of interest

Studies comparing a common dose of one agent versus a unlicensed dose of comparator

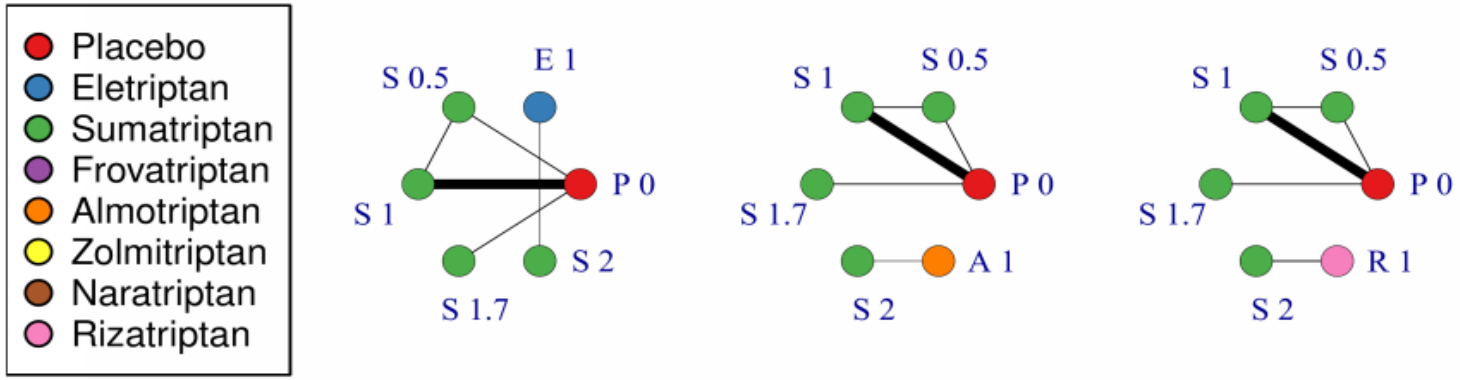
Not connected

Studies comparing a common dose of one agent versus comparator other doses.

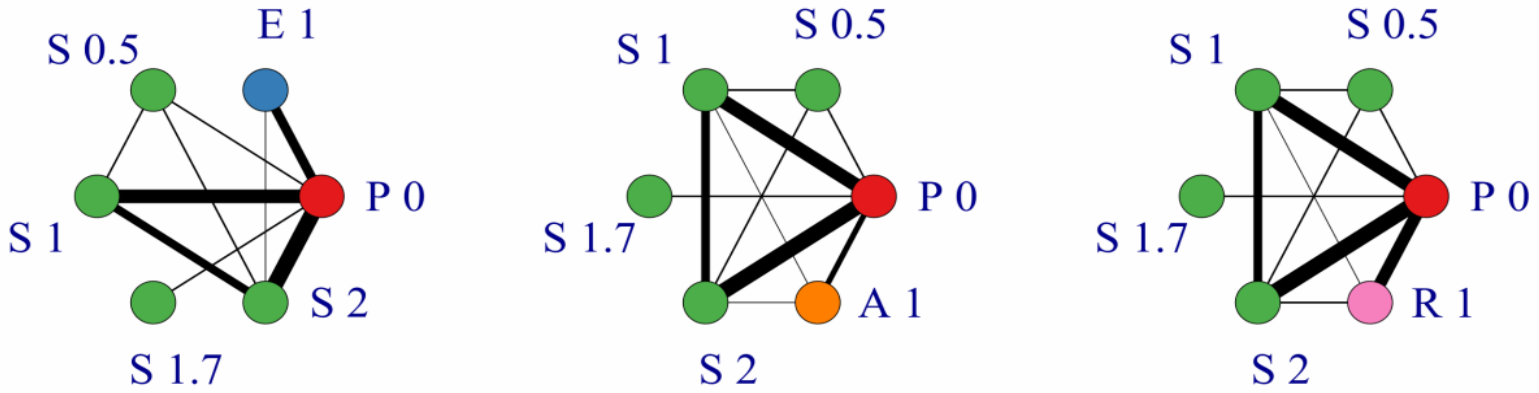


# SCENARIO 3

Disconnected network




Augmented network



# SCENARIO 3 RESULTS

**Table 3** Model Fit Statistics for Selected MBNMA and NMA Models in Each Data Set Analyzed in Scenario 3

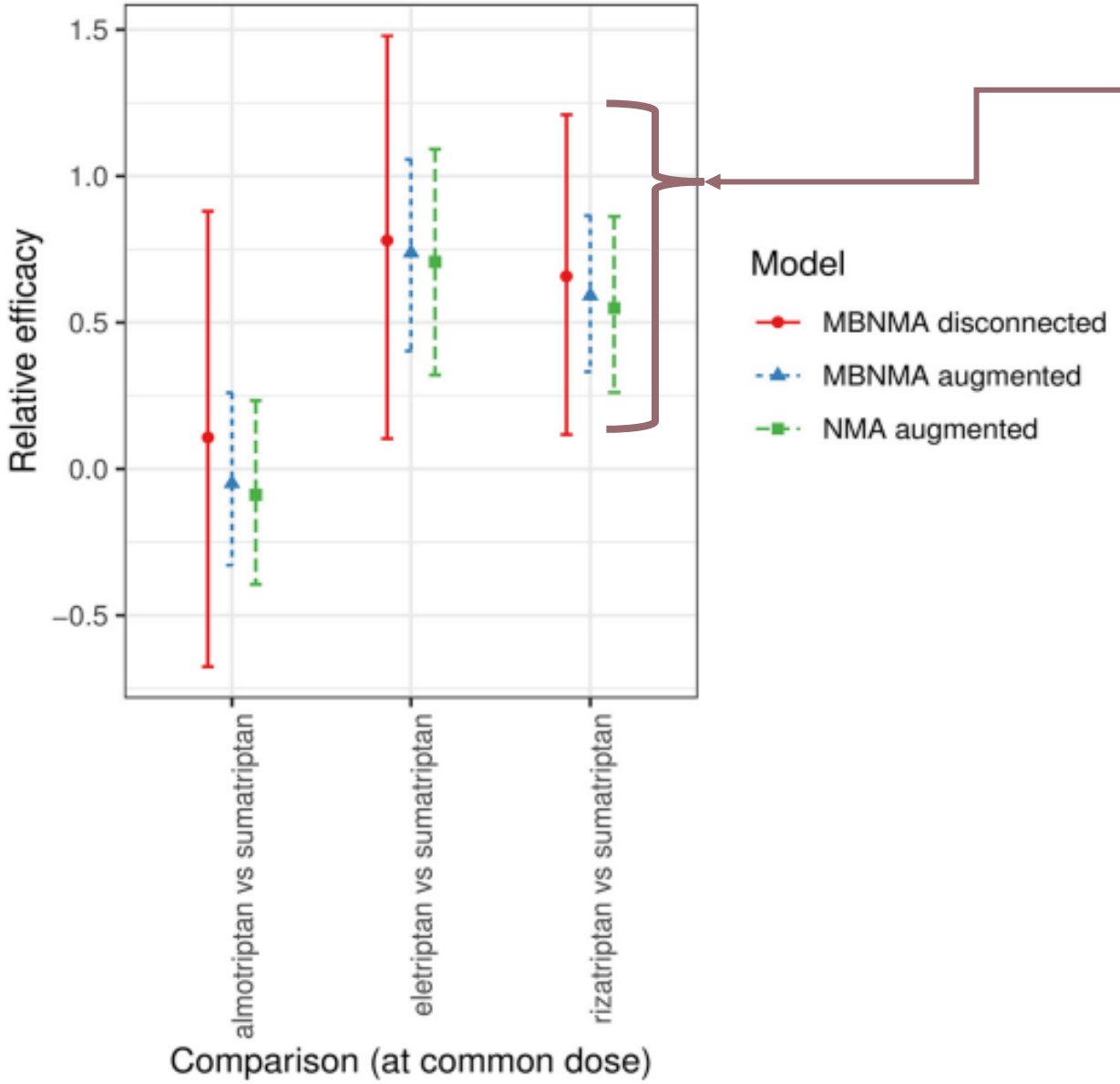
| Dataset Number | Data Set | Agent 1 | Agent 2 | No. of Data Points | Residual Deviance | DIC[a] | pD[b] | Model | Dose-Response Function | Treatment Effects | Between-Study SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Initial | Almotriptan | Sumatriptan | 38 | 37.5 | 66.6 | 29.1 | MBNMA | Exponential | Random | 0.30 (0.10–0.54) |
| 1 | Augmented | Almotriptan | Sumatriptan | 74 | 74.3 | 127.5 | 53.3 | MBNMA | Exponential | Random | 0.28 (0.16–0.44) |
| 1 | Augmented | Almotriptan | Sumatriptan | 74 | 75.3 | 128.6 | 53.3 | NMA | NA | Random | 0.27 (0.12–0.42) |
| 2 | Initial | Eletriptan | Sumatriptan | 38 | 37.2 | 66.8 | 29.6 | MBNMA | Exponential | Random | 0.29 (0.11–0.54) |
| 2 | Augmented | Eletriptan | Sumatriptan | 80 | 81.1 | 141.0 | 59.8 | MBNMA | Exponential | Random | 0.35 (0.22–0.52) |
| 2 | Augmented | Eletriptan | Sumatriptan | 80 | 81.0 | 142.5 | 61.6 | NMA | NA | Random | 0.36 (0.22–0.53) |
| 3 | Initial | Rizatriptan | Sumatriptan | 40 | 38.6 | 69.2 | 30.6 | MBNMA | Exponential | Random | 0.28 (0.11–0.53) |
| 3 | Augmented | Rizatriptan | Sumatriptan | 87 | 89.0 | 152.9 | 63.9 | MBNMA | Exponential | Random | 0.32 (0.21–0.48) |
| 3 | Augmented | Rizatriptan | Sumatriptan | 87 | 89.5 | 154.1 | 64.6 | NMA | NA | Random | 0.32 (0.20–0.47) |

[a] DIC: deviance information criterion = pD + residual deviance.
[b] pD: The effective number of parameters calculated using the Kullback-Leibler divergence[30] for model-based network meta-analysis (MBNMA) and the plugin method[29] for NMA.

NA: not applicable

- Exponential MBNMA models with random treatment effects were selected In disconnected networks (Initial) and augmented
- Random effects models were selected in all data sets for NMA models

# SCENARIO 3 RESULTS




- **Still High uncertainty** in disconnected MBNMA models
- Estimates in augmented data sets were **within the 95% CrIs** of those from MBNMAs in the disconnected data sets suggesting that **results were in agreement**

- **For Augmenting data**
- **MBNMA and NMA estimates** were very similar
- **Higher precision** in **MBNMA estimates**

# *DISCUSSION*

- The study illustrate scenarios in which dose response MBNMA can be used to strengthen the NMA method by either increasing precision or connecting the disconnected networks.
- This can be done by adding evidence of unlicensed doses and modeling a functional dose repose relationship.
- Connection can be done by linking different doses of the same agent along the dose response curve
- Or link different agents by extrapolating a placebo response.
- In HTAs with connected networks, whereby multiple doses are of interest,  using MBNMA can be of benefit, ↑ precision

# *DISCUSSION*

- In disconnected networks (scenarios 2 and 3), MBNMA estimates were consistent with NMA estimates from augmented datasets.
- Although MBMNA could be estimated In situation where there is no common comparators between 2 agents (scenario 2), a complex dose-response function could not be fitted due to lack of information of different dose of each agent.
- In scenario 3 (one of the agents of interest were compared to the unlicensed dose of another agent) MBNMA was able to link the agents at licensed dose.
- In this scenario, estimates from the disconnected and augmented data sets agreed, could be due to availability of evidence of different doses of agents connected via dose-response relationship.

# *DISCUSSION*

- MBNMA approach uses RCTs only and does not violate the randomization in RCTs thus provide unbiased estimates.
- Can be fitted using aggregate data only, no need for individual patient data

Provided that Important assumptions of:

- Consistency assumption
- dose-response function correct specification are met

# *OTHER METHODS FOR DISCONNECTED NETWORKS*

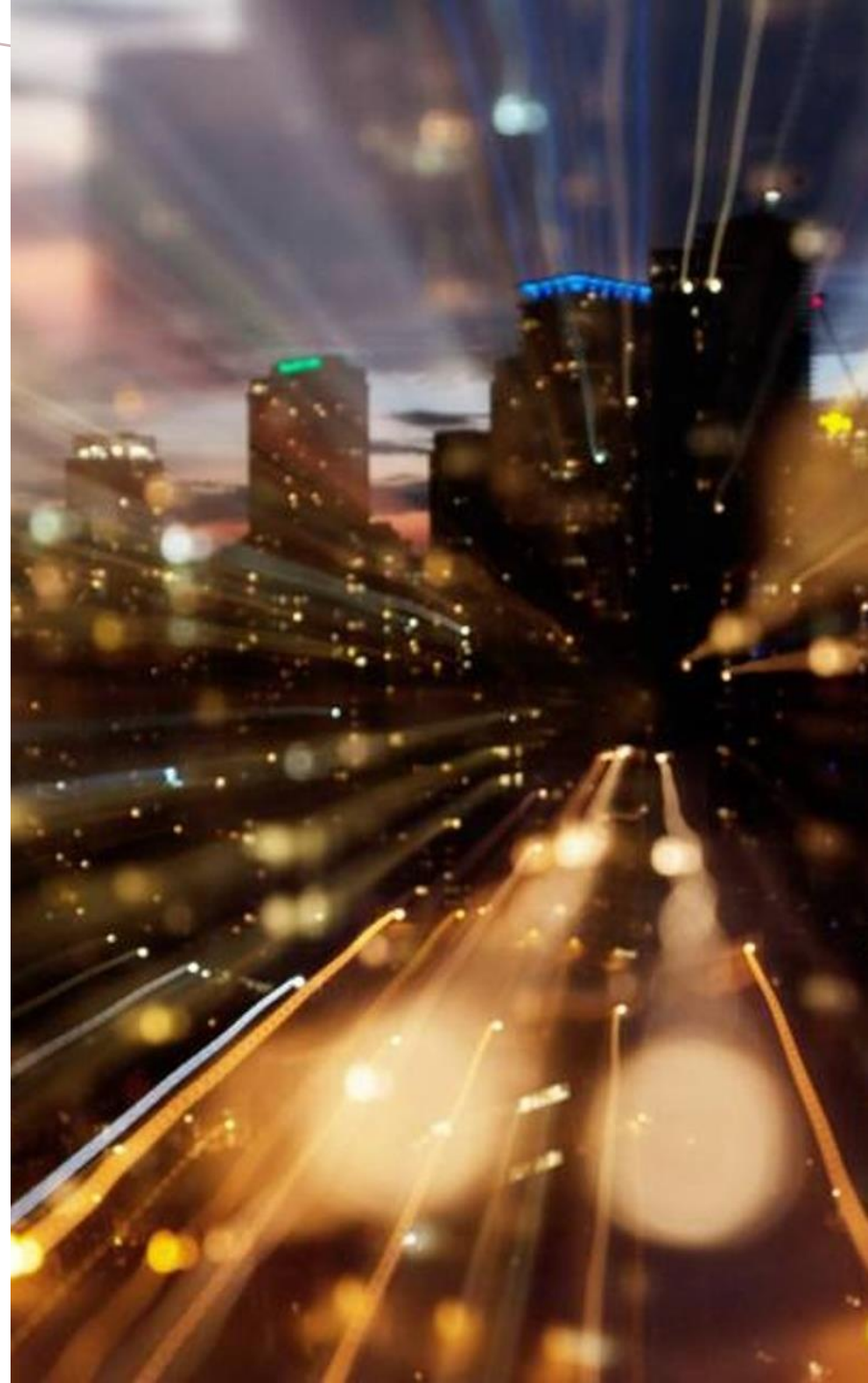
- Model-based meta-analysis (MBMA)
- Predict effect of reference treatment by random effects
- Population adjustment methods (e.g matched adjusted indirect comparisons or simulated treatment comparisons)
- Component network meta-analysis
- A joint analysis using multivariate NMA
- Time-course MBNMA
- Assuming a common or exchangeable effect among similar treatments

# *LIMITATIONS*

- Dose-response MBNMA is sensitive to misspecification of the dose response function.
- Complex functions like Emax model require data on multiple doses of different agents to be able to estimate them.
- In case there is only one dose + placebo OR 2 doses without placebo for each agent, only simple functions like linear or exponential can be fitted.
- Model fit statistics cannot help distinguish between simple dose response function models.
- Simulation studies to explore the performance of MBNMA models for different evidence structures would be a useful area for further work.

# *CONCLUSIONS*

- **NMA** requires connected treatment networks
- **MBNMA** reconnects disconnected networks using **dose–response relationships** when evidence on multiple doses of agents is available.
- In augmented data sets, the MBNMA and NMA estimates were in agreement.
- MBNMA adds an extra assumption: **the dose–response relationship is correctly specified** (can be checked via model fit)
- MBNMA can use **aggregate data** and often provides **greater precision** than NMA when multiple doses exist
- Requires **data on multiple doses** for each treatment to work effectively



# *THANK YOU*