METRUM RESEARCH GROUP

Meta-analysis: Choosing the right tool for the job

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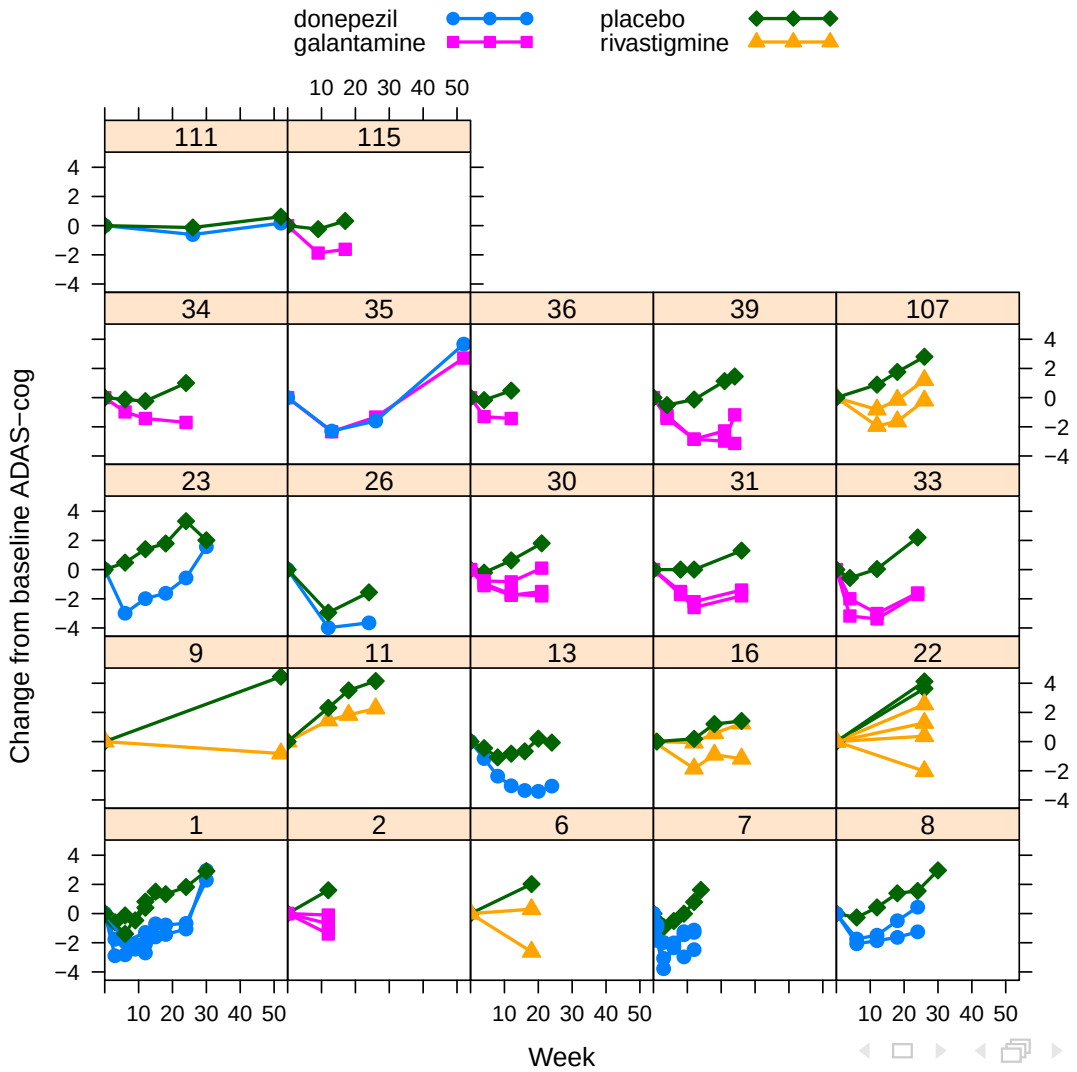
Setting

- Suppose we are developing a new compound for the symptomatic treatment of Alzheimer's disease
- We are interested in understanding the efficacy of the currently marketed treatments
- We perform a systematic review of the literature and come up with 22 controlled clinical trials

Drug	# Studies
Donepezil	8
Galantamine	9
Rivastigmine	6

The data are available at www.opendiseasemodels.org.

Longitudinal ADAS-cog data (ignoring dose)



There are a number of potential objectives of interest

- What are the relative effects of marketed doses at Month 6?
  - Donepezil 10 mg vs. placebo
  - Donepezil 10 mg vs. Galantamine 24 mg
  - Donepezil 10 mg. vs. Rivastigmine
- What are the effects at other time points (e.g., Months 1, 3, 12)?
- What are the effects at other doses?
- What is the rate of change (disease progression) in this patient population?
- What is the effect and/or rate of change in different populations?

Uses of the meta-analysis results

Ultimately we want to be able to use these analyses to inform decisions

- Trial design (e.g., parallel vs. cross-over; sample size; adaptive vs. fixed designs)
- Threshold for Go/No-Go decisions
- Comparative effectiveness

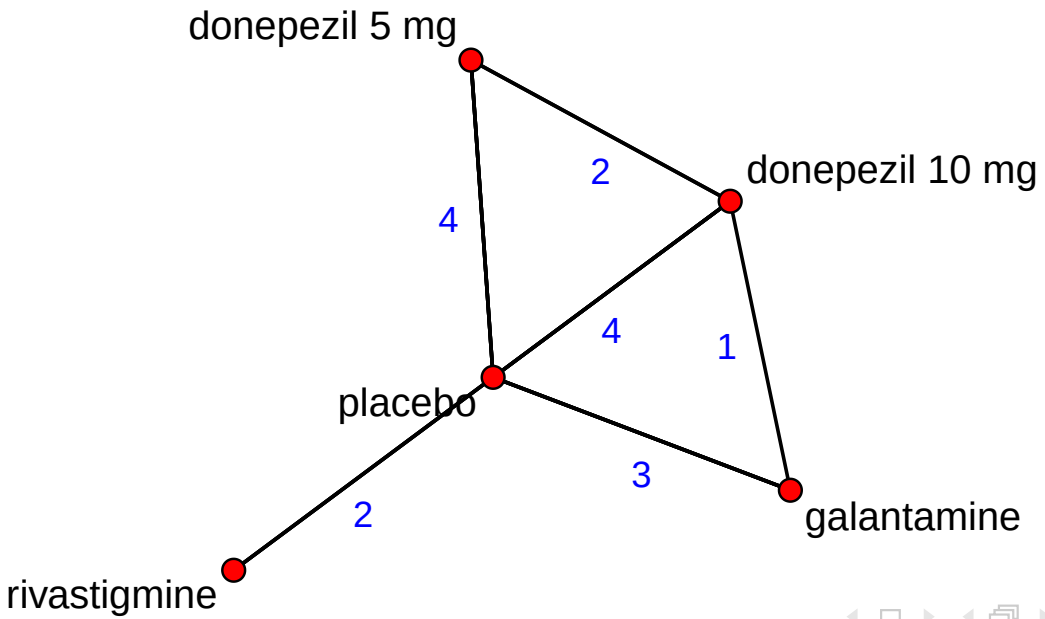
The objectives we have and how we want to use them should dictate the type of models we fit

- Traditional pairwise comparison meta-analysis
- Network meta-analysis
- Model-based meta-analysis

One approach will not necessarily be the best for all situations

Pairwise Meta-analysis

- Pairwise meta-analysis is the classic method for combining summary level information across multiple studies (see Whitehead, 2002, for a good reference).
- It enables pooling of *direct* evidence across studies of two treatments



Pairwise random-effects meta-analysis model

For a set of studies comparing treatments $j = 1$ and $j = 2$, the basic pairwise random-effects meta-analysis model is

$$Y_{ij} = \mu_i + \delta_i I_{[j=2]} + \epsilon_{ij}$$
$$\delta_i \sim N(\Delta, \tau^2)$$
$$\epsilon_{ij} \sim N(0, s_{ij}^2)$$

where
- Y_{ij} and s_{ij} are data
- the μ_i are fixed study-level effects in the reference group,
- $i = 1, \ldots,$ # of studies
- $j = 1$ for the reference group and $j = 2$ for the experimental group.

The primary focus of inference is usually on Δ and τ^2.

- In the context of the AD dataset, Y_{ij} is the change from baseline ADAS-cog score in group j of study i.
- We will estimate effects for Donepezil 5 mg, Donepezil 10 mg, Galantamine 24 mg, and Rivastigmine ($\geq$ 6 mg),
- Thus, we would fit 4 separate models (one for each possible comparison to placebo).
- Then we have eight parameters of interest

Drug group	**Mean**	**Variance**
Donepezil 5 mg	Δ_{D5}	τ^2_{D5}
Donepezil 10 mg	Δ_{D10}	τ^2_{D10}
Galantamine 24 mg	Δ_G	τ^2_G
Rivastigmine	Δ_R	τ^2_R

Key assumptions of the pairwise meta-analysis model

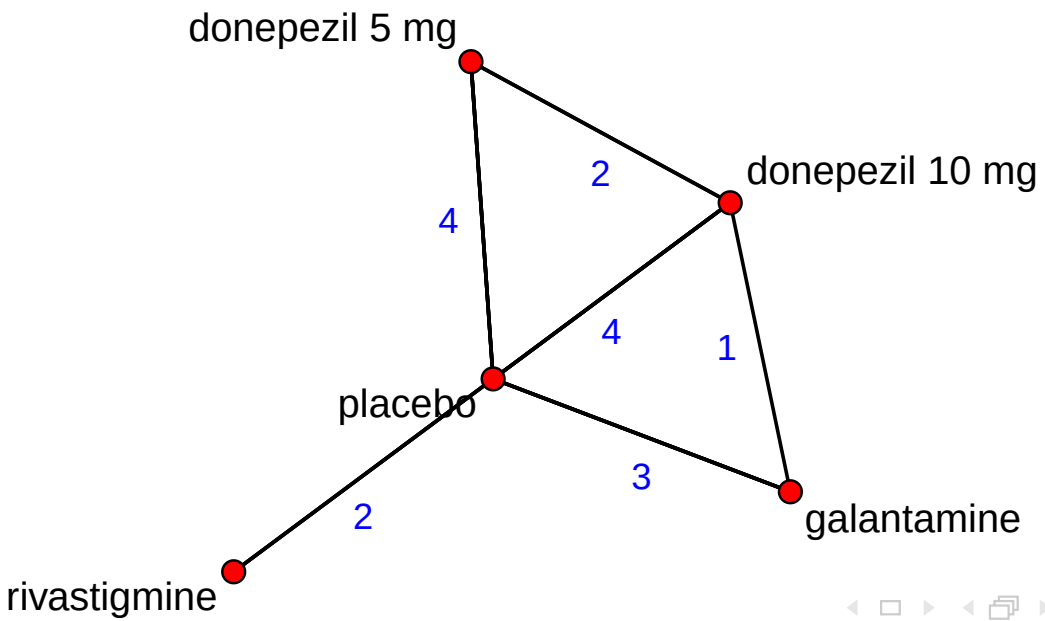
Assumptions

- No model assumed for μ_i
- Study-specific treatment effects (δ_i) are exchangeable across studies
- Exchangeability is across the set of studies relevant for the comparison of interest, not across all studies

Exchangeability $\approx$ the study-specific effects come from a common distribution, e.g., $\delta_i \sim N(\Delta, \tau^2)$.

Network Meta-analysis

- Network meta-analysis (aka mixed treatment comparison) is an extension to traditional pairwise meta-analysis (Lumley 2002; Lu and Ades, 2004).
- It enables pooling of *direct and indirect* evidence in one model (12 studies).



- A network meta-analysis model for the mean change from baseline ADAS-cog data ($Y_{i,j}$) can be expressed as

$$Y_{i,j} = \mu_{i,P} + \delta_{i,j} + \epsilon_{i,j}$$

where

$$\delta_{i,j} \sim N(\Delta_j, \tau_j^2) \qquad j \neq P$$

$$\epsilon_{i,j} \sim N(0, s_{i,j}^2)$$

and i indexes study and $j \in \{P, D5, D10, R, G\}$ indexes the treatment group

- Usually assume that $\tau_j^2 = \tau^2$

Key assumptions of network meta-analysis model

Dias et al. (2011) highlight the key assumptions of the network meta-analysis model:

Assumptions

- No model assumed for $\mu_{i,P}$
- Study-specific treatment effects, $\delta_{i,j}$ are exchangable across *all* studies (i.e., even studies without treatment *j*).
- If we assume $\tau_j^2 = \tau^2$, then Corr$(\delta_{1j}, \delta_{1j'}) = 0.5$ (Lu and Ades, 2009)

The exchangeability assumption is crucial

- Enables coherent indirect comparisons of two treatments with no direct evidence
- Enables a coherent synthesis of direct and indirect evidence
  - E.g., Trials comparing drug *A* vs. drug *B* with trials comparing drug *A* vs. placebo and drug *B* vs. placebo
- The consistency equations (e.g., $\Delta_{D10,D5} = \Delta_{D10} - \Delta_{D5}$) follow directly from this assumption
  - The consistency equations are what allow us to make statistically coherent indirect comparisons

If consistency in the network doesn't hold true, this may be due to a violation of the exchangeability assumption.

See Dias et al (2011) for more details.

Model-based meta-analysis

- There is no single method for performing a model-based meta-analysis
- Models will depend on data and objectives.
- Models can be landmark (single time-point) or longitudinal; dose-response or not.
- This approach has been much less rigorously defined and developed than traditional and Network MA.
- Many examples in the literature

For the ADAS-cog data, we will use a model very similar to the longitudinal dose-response model published by Ito et al. (2009):

$$Y_{ijk} = \eta_{1i} + \alpha_i \cdot t_{ijk} + \epsilon_{ijk}$$

where

$$\alpha_i = \alpha + \eta_{2i}$$

i indexes study, j indexes treatment arm, k indexes visit

Emax_j, ET50_j, and θ_j are drug-specific parameters.

$$\eta_i = (\eta_{1i}, \eta_{2i}, \eta_{3i})^T \sim MVN(\mathbf{0}, \Omega)$$
$$\epsilon_{ijk} \sim N(0, \sigma^2 / N_{ijk})$$

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$$Y_{ijk} = \eta_{1i} + \alpha_i \cdot t_{ijk} + \beta \cdot \left(e^{-Keq \cdot t_{ijk}} - e^{-Kel \cdot t_{ijk}} \right) + \epsilon_{ijk}$$

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$$Y_{ijk} = \eta_{1i} + \alpha_i \cdot t_{ijk} + \beta \cdot \left(e^{-Keq \cdot t_{ijk}} - e^{-Kel \cdot t_{ijk}} \right) + \frac{\text{Emax}_j \cdot \left(\frac{d_{ijk}}{RD_j} \right)^{\theta_j} \cdot t_{ijk}}{\text{ET50}_j \cdot e^{\eta_{3i}} + t_{ijk}} + \epsilon_{ijk}$$

where

$$\alpha_i = \alpha + \eta_{2i}$$

i indexes study, j indexes treatment arm, k indexes visit

Emax_j, ET50_j, and θ_j are drug-specific parameters.

$$\eta_i = (\eta_{1i}, \eta_{2i}, \eta_{3i})^T \sim MVN(\mathbf{0}, \Omega)$$
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Estimating differences with the MBMA model

The traditional and network meta-analysis models, model the difference between groups directly.

With the MBMA model, we derive these from the model. For example, at Month 6

$$\delta_{i,D10} = \frac{\text{Emax}_D \cdot \left(\frac{10}{5}\right)^{\theta_D} \cdot 6}{\text{ET50}_D \cdot e^{\eta_{3i}} + 6}$$

and

$$\Delta_{D10} = \textit{median}[\delta_{i,D10}] = \frac{\text{Emax}_D \cdot \left(\frac{10}{5}\right)^{\theta_D} \cdot 6}{\text{ET50}_D + 6}$$

Assumptions of MBMA

Assumptions

- Structural form of model
- Placement of random effects
- Study-level vs. treatment arm-level random effects
- Exchangeable random effects (across the set of studies and/or arms)
- Other implicit assumptions depending on the model
  - E.g., for the ADAS-cog model, the correlation of difference from placebo for two arms in the same study is 1.0 (as compared to 0.5 for the network meta-analysis model).

Assumptions can bring benefits

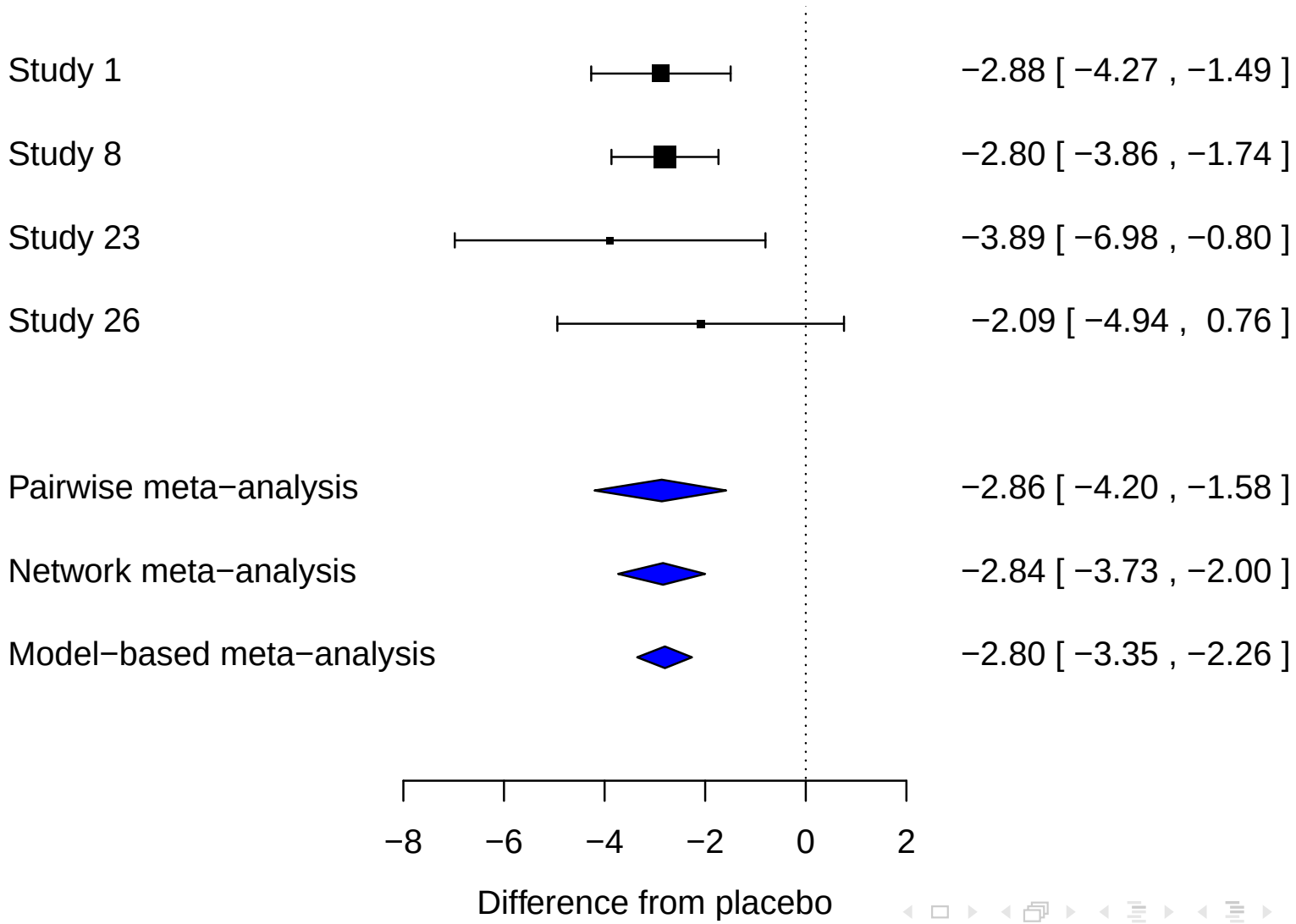
- Incorporate regimens with changing doses
- Pool across diseases
- Pool across times/doses that don't match
- Pool across study design differences
- Pool across different endpoints
- etc.

Analysis of ADAS-cog data

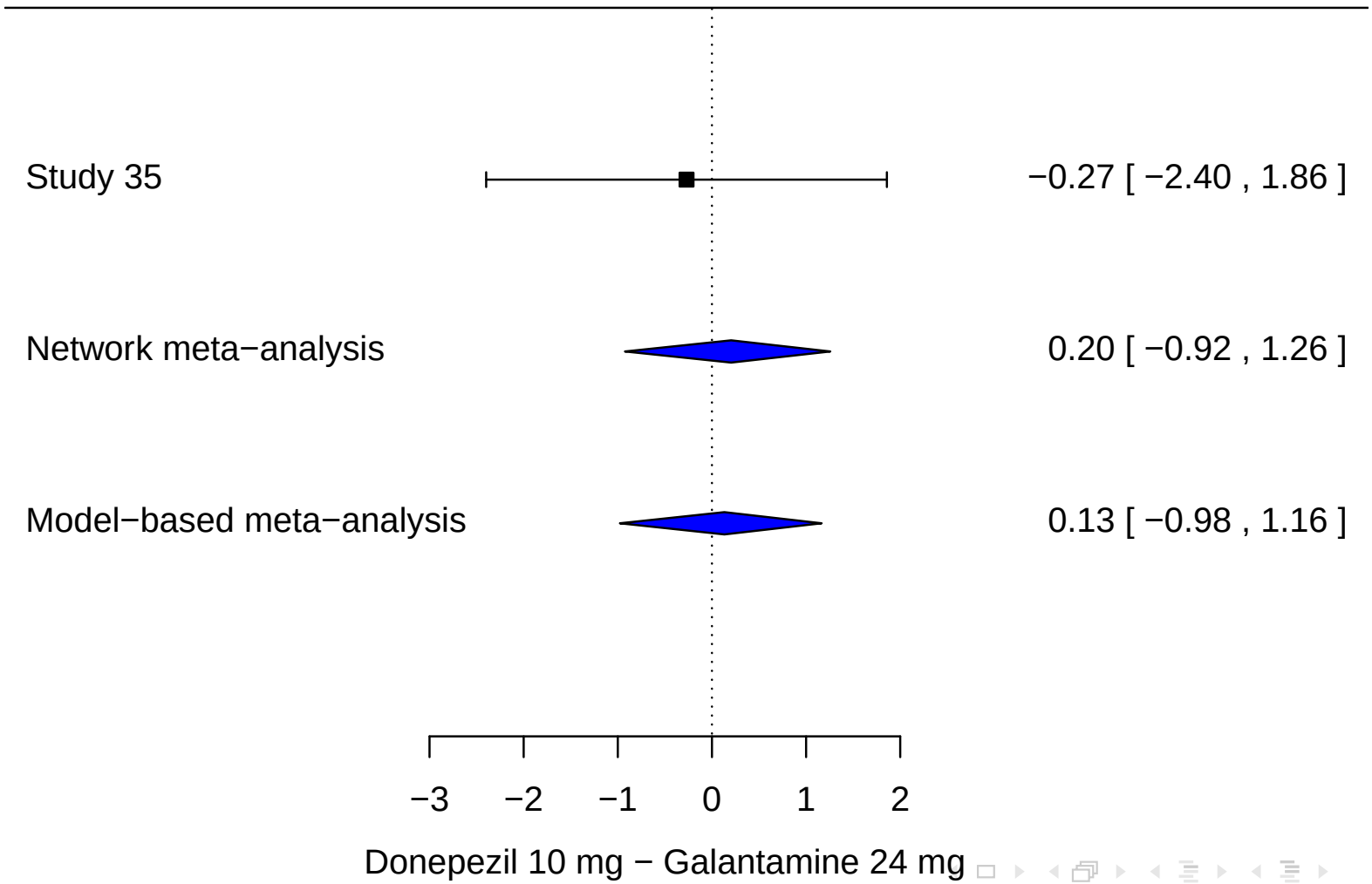
Compare estimates and uncertainty from various models and approaches

- Donepezil 10 mg vs. placebo at Month 6
  - Direct and indirect evidence of effect
- Donepezil 10 mg vs Galantamine 24 mg at Month 6
  - Limited direct evidence + indirect evidence
- Donepezil 10 mg vs. Rivastigmine at Month 6
  - Indirect evidence only
- Effects of donepezil at doses other than 5 and 10 mg
  - Indirect evidence via the model

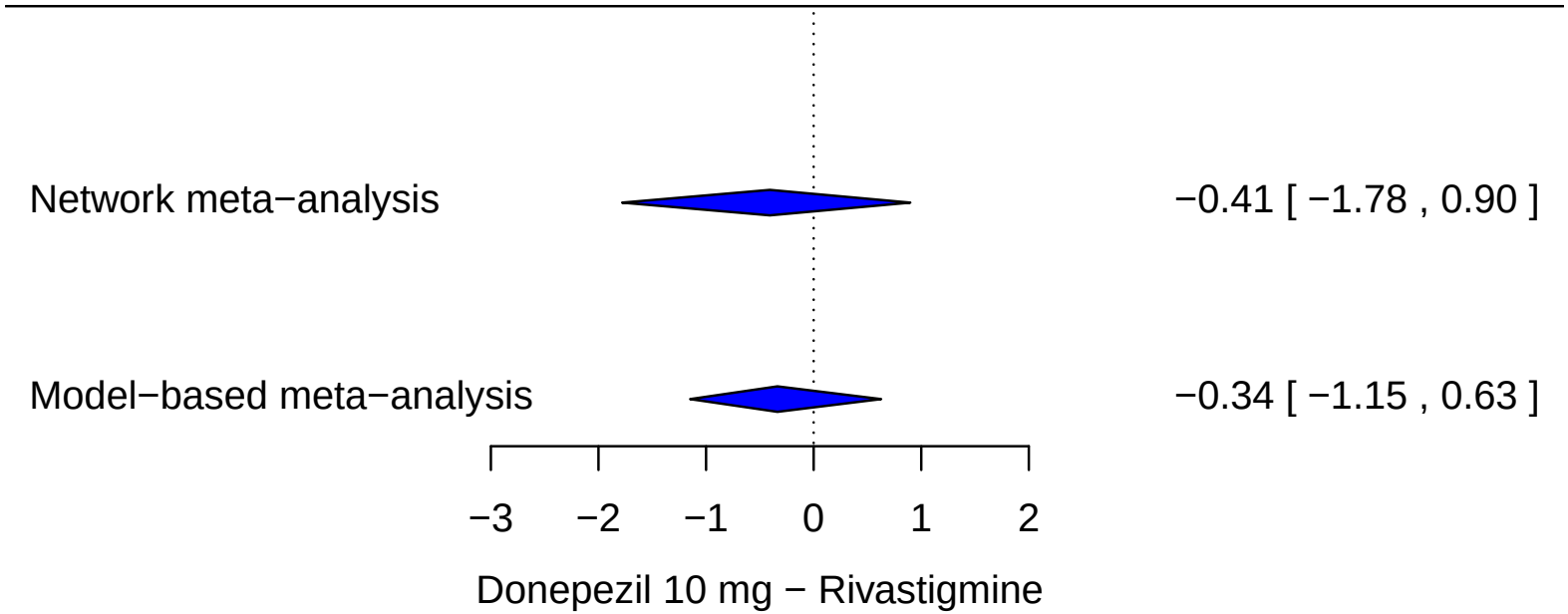
Donepezil 10 mg vs. Placebo at Month 6



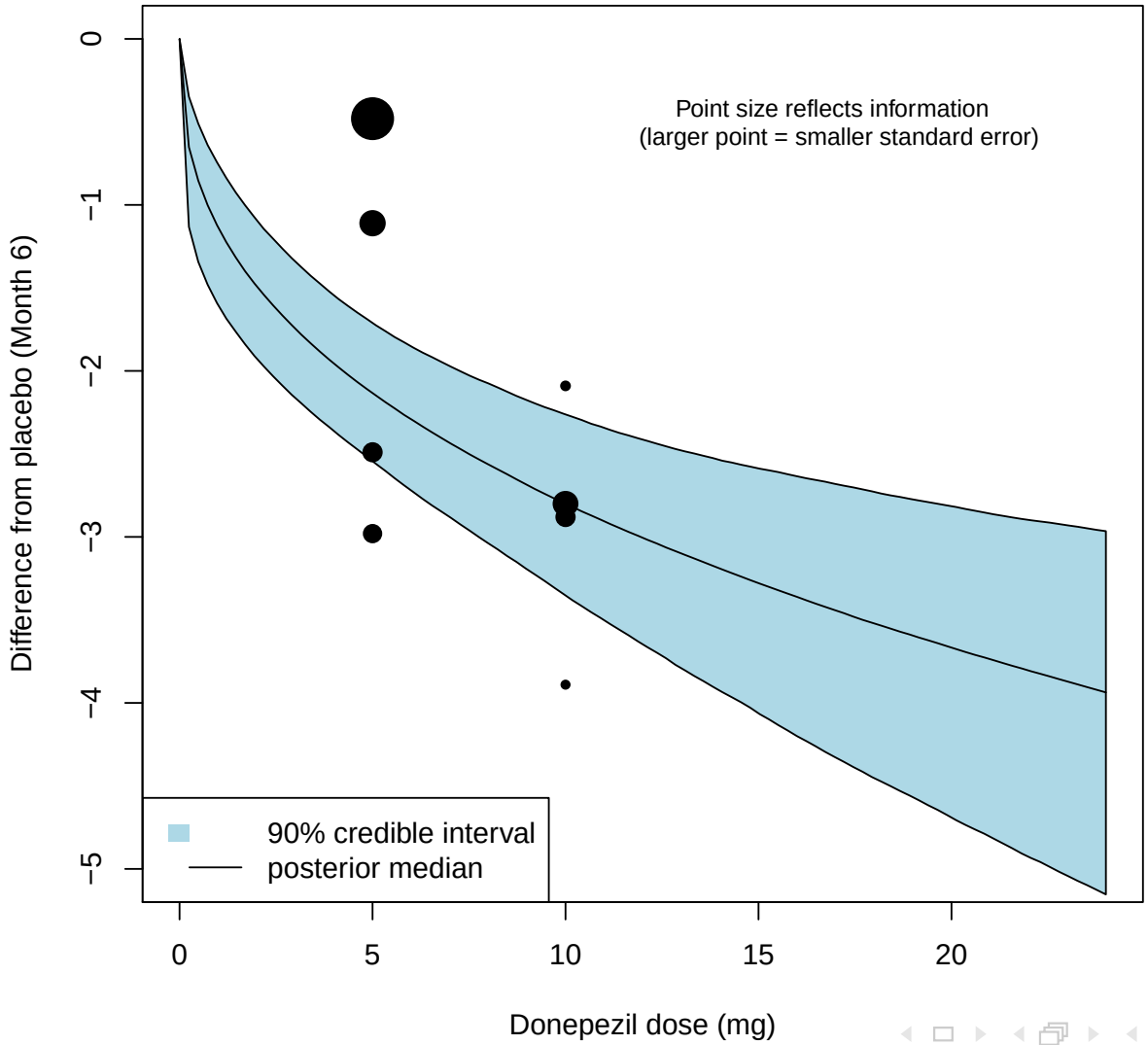
Donepezil 10 mg vs. Galantamine at Month 6



Donepezil 10 mg vs. Rivastigmine at Month 6



Donepezil dose response at Month 6



Conclusions

- We should not take a 'one-model-fits-all' approach to meta-analysis
- There are times when a simpler model (with well understood assumptions) may be preferred to a model-based meta-analysis
  - Even simple meta-analysis models make assumptions

	Pairwise MA	**Network MA**	**MBMA**
Estimating difference between groups			
- Inference based on direct evidence	✓	✓	✓
- Inference based on indirect evidence		✓	✓
Extrapolation/interpolation in dose, time, etc.			✓

Conclusions

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- There are times when a simpler model (with well understood assumptions) may be preferred to a model-based meta-analysis
  - Even simple meta-analysis models make assumptions

	Pairwise MA	**Network MA**	**MBMA**
Donepezil 10 mg vs. Placebo	✓	✓	✓
Donepezil 10 mg vs. Galantamine 24 mg		✓	✓
Disease progression			✓
Dose response			✓

Conclusions(2)

- When other aspects other than simple treatment group differences are of interest, a MBMA may provide more insight and utility
  - E.g., estimating disease progression rate or duration of placebo effect
  - Simulation to evaluate clinical trial designs or decision rules
  - Comes with more (and less transparant) assumptions

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References

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Back-up Slides

Subset of studies	# of studies
All controlled studies	22
+ Month 6 data & 'typical' doses	15
+ poolable designs	12

'Typical' doses: 5 & 10 mg donepezil, 24 mg Galantamine, $\geq$ 6 mg Rivastigmine

If other time points and doses tell us something about the effects at Month 6 for the doses of interest, we are limiting ourselves if we restrict to the smaller set of data . . .

- A random effects network meta-analysis model for the mean change from baseline ADAS-cog data ($Y_{i,j}$) can be expressed as

$$Y_{i,j} = \mu_{i,P} + \delta_{i,j} + \epsilon_{i,j}$$

where

$$\delta_{i,j} \sim N(\Delta_j, \tau_j^2) \qquad j \neq P$$

and i indexes study and $j \in \{P, D5, D10, R, G\}$ indexes the treatment group

- Usually assume that $\tau_j^2 = \tau^2$

- The parameters $\Delta_j, j \neq P$ are the *basic* parameters of the model; from these, the other differences can be derived.
  - E.g., the difference between the effect of donepezil 10 mg and 5 mg is $\Delta_{D10} - \Delta_{D5}$

Multi-arm studies

- For studies with more than 2 treatment groups, we need to account for the correlation between $\delta_{i,j}$ and $\delta_{i,j'}$.
- Under the assumption that $Var(\delta_{i,j}) = \tau^2$ for all i and j, it can be shown that the correlation is 0.5.
- For example, for a trial with placebo, donepezil 5 and 10 mg:

$$\delta_i = (\delta_{i,D5}, \delta_{i,D10}) \sim N(\Delta_i, \Omega_i)$$

where

$$\Delta_i = (\Delta_{D5}, \Delta_{D10})$$

$$\Omega_i = \tau^2 \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}$$