



Lecture 2

Indirect and mixed treatment comparisons

Adriani Nikolakopoulou

Network meta-analysis

A project-based course using R

Kea island, April 2018

Standard ('pairwise') meta-analysis

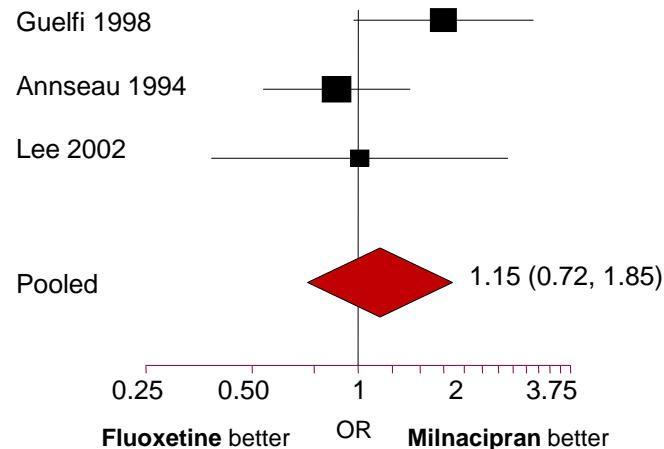
Meta-analysis of randomized control trials (RCTs) is a statistical methodology used to combine results of different studies carried out to answer the same clinical question

It is a key ingredient in today's comparative effectiveness research in evidence-based medicine

Example:

Three RCTs comparing
two antidepressants

Meta-analysis comparing two antidepressants for major depression



... however ...

- Traditional meta-analytical techniques can only compare two treatments
- Thus their usefulness is limited when three or more competing treatments for the same condition are present
- In such cases pairwise meta-analysis cannot give a definite answer as to which treatment works best

Medical decision making

Blocked ears, earwax removal techniques:

- **Cerumol, Sodium bicarbonate, Olive oil, Dry and wet irrigation, TP, Self irrigation, Irrigation by nurse, Endoscopic and microscoping de-waxing**
- *Is any of the interventions effective?*
- *How **much more** effective they are compared to no intervention?*
- *Are some interventions more effective than other?*



The safety and effectiveness of different methods of earwax removal: a systematic review and economic evaluation

AJ Clegg, E Loveman, E Gospodarevskaya,
P Harris, A Bird, J Bryant, DA Scott,
P Davidson, P Little and R Coppin



- Cerumol
- Sodium bicarbonate
- Olive oil
- Dry and wet irrigation
- TP
- Self irrigation
- Irrigation by nurse
- Endoscopic and microscoping de-waxing

Results: Twenty-six clinical trials conducted in primary care (14 studies), secondary care (8 studies) or other care settings (4 studies), met the inclusion criteria for the review – 22 RCTs and 4 CCTs. The range of interventions included 16 different softeners, with or without irrigation, and in various different comparisons. Participants, outcomes, timing of intervention, follow-up and methodological quality varied between studies. On measures of wax clearance Cerumol, sodium bicarbonate, olive oil and water are all more effective than no treatment; triethanolamine polypeptide (TP) is better than olive oil; wet irrigation is better than dry irrigation; sodium bicarbonate drops followed by irrigation by nurse is more effective than sodium bicarbonate drops followed by self-irrigation; softening with TP and self-irrigation is more effective than self-irrigation only; and endoscopic de-waxing is better than microscopic de-waxing. AEs appeared to be minor and of limited extent. Results of the



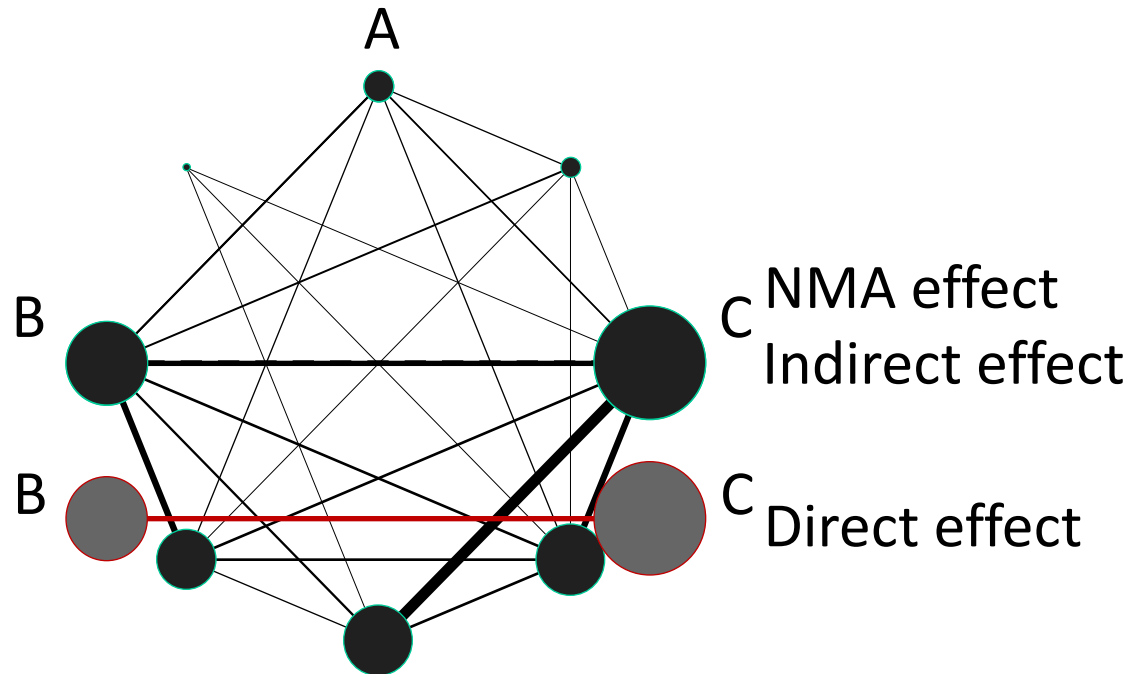
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followed by irrigation by nurse is more effective than

The results from many pairwise meta-analyses are not
useful when you want to compare many treatments!

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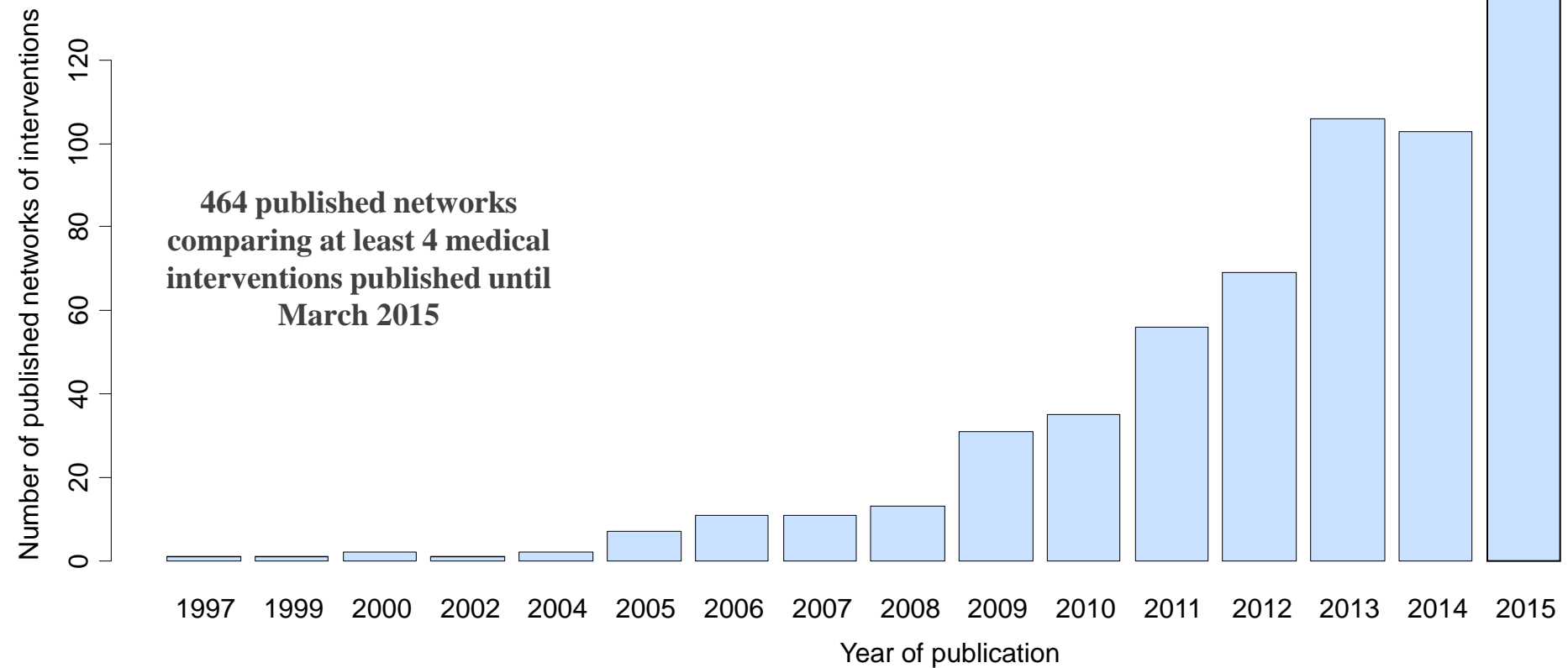
Idea of indirect comparisons



Advantages of NMA

- Utilizes all available evidence
- Enables comparison of treatments that have never been compared in individual studies
- Usually gives estimates with increased precision compared to standard meta-analysis
- It provides a ranking of the treatments

Network meta-analysis is becoming increasingly popular



(Petropoulou et al. Journal of Clinical Epidemiology, 2016)

Indirect comparison

- If we know how much taller is **C to A** and how much taller is **B to A**, we know how much taller is **C compared to B**



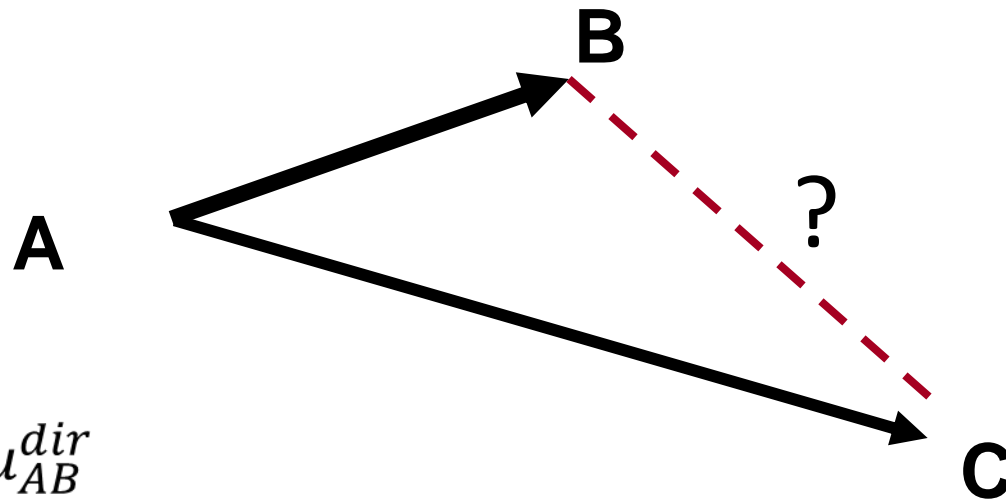
- For any pair B and C:

typical (or mean) advantage of **C over B** =
advantage of **C over A** – advantage of **B over A**

➤ *If C is 10 meters higher than A and B is 3 meters higher than A
then C is $10 - 3 = 7$ meters higher than B*

Indirect comparison

We can obtain an *indirect estimate* for B vs C from RCTs comparing A vs B and A vs C:

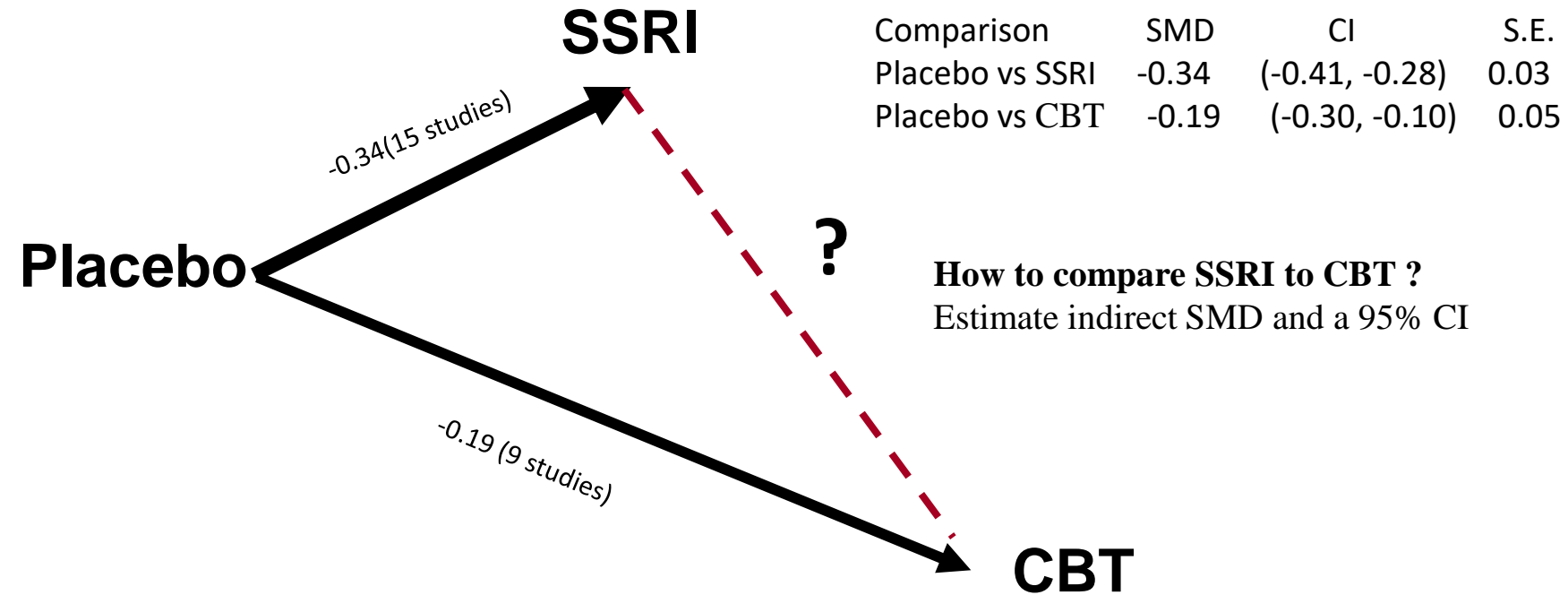


$$\mu_{BC}^{ind} = \mu_{AC}^{dir} - \mu_{AB}^{dir}$$

$$var(\mu_{BC}^{ind}) = var(\mu_{AC}^{dir}) + var(\mu_{AB}^{dir})$$

$$95\% \text{ C.I. } \mu_{BC}^{ind} \pm 1.96 \sqrt{var(\mu_{BC}^{ind})}$$

Fictional example: CBT vs SSRI for depression



$$SMD_{CBTvSSRI}^{ind} = -0.34 - (-0.19) = -0.15 \quad var(SMD_{CBTvSSRI}^{ind}) = 0.03^2 + 0.05^2 = 0.0034$$

$$SMD_{CBTvSSRI}^{ind} \pm 1.96 \sqrt{var(SMD_{CBTvSSRI}^{ind})} = -0.15 \pm 1.96 \sqrt{0.0034} = (-0.26, -0.04)$$



Cochrane
Library

Cochrane Database of Systematic Reviews

Haloperidol alone or in combination for acute mania (Review)

Cipriani A, Rendell JM, Geddes J

[Intervention Review]

Haloperidol alone or in combination for acute mania

Andrea Cipriani¹, Jennifer M Rendell², John Geddes²

¹Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona, Italy.

²Department of Psychiatry, University of Oxford, Oxford, UK

Contact address: Andrea Cipriani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Policlinico "G.B.Rossi", Piazzale L.A. Scuro, 10, Verona, 37134, Italy. andrea.cipriani@univr.it.
andrea.cipriani@psych.ox.ac.uk.

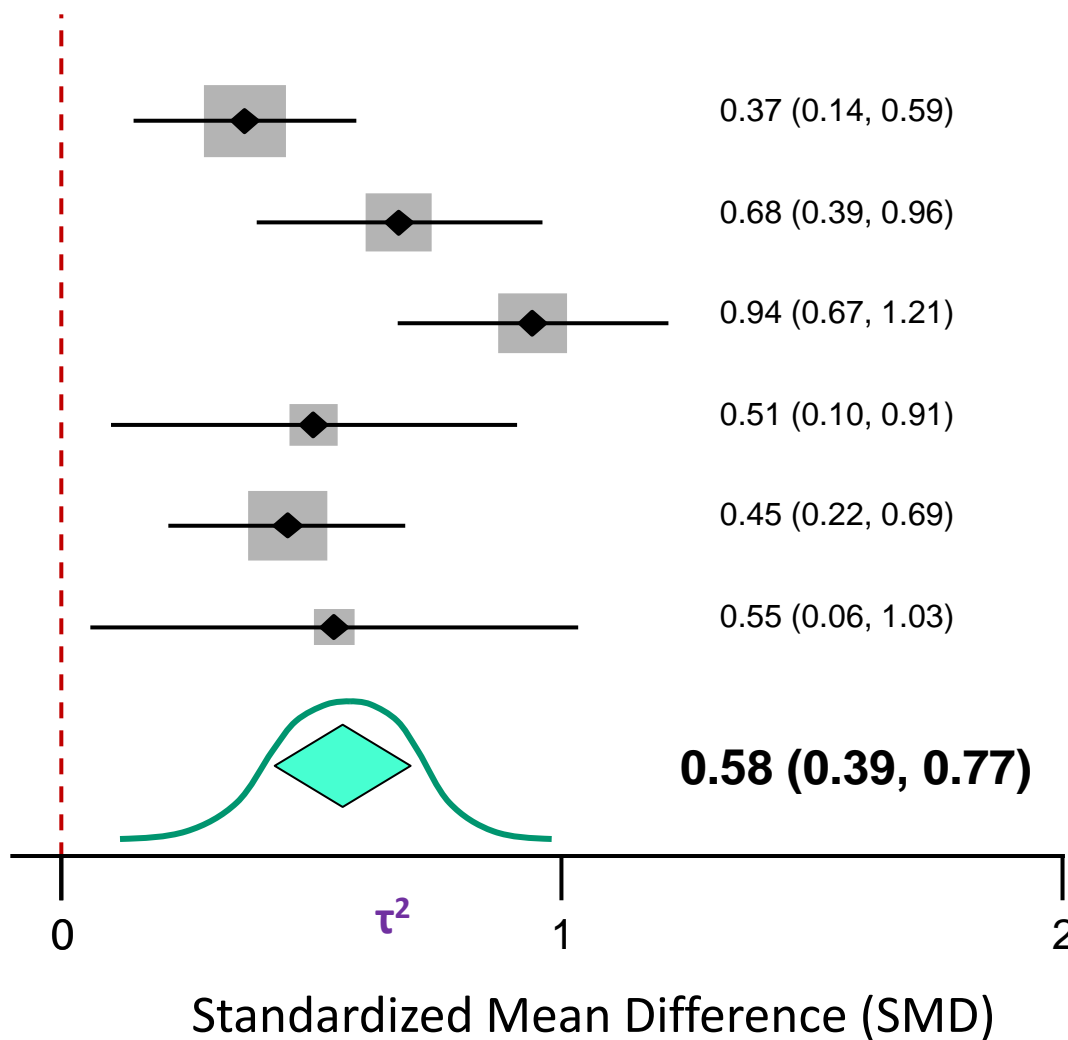
Editorial group: Cochrane Common Mental Disorders Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Review content assessed as up-to-date: 22 May 2006.

Citation: Cipriani A, Rendell JM, Geddes J. Haloperidol alone or in combination for acute mania. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD004362. DOI: 10.1002/14651858.CD004362.pub2.

HAL vs PLA for reducing manic symptoms

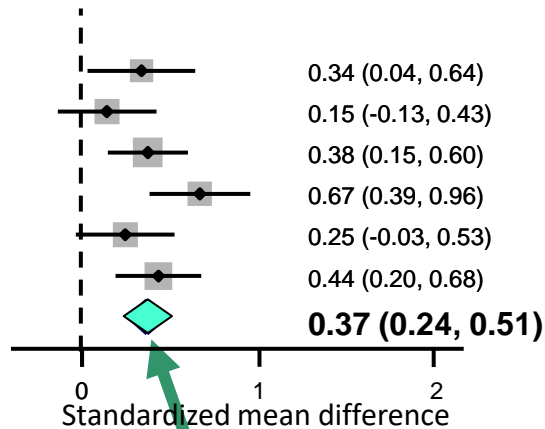


Six eligible studies

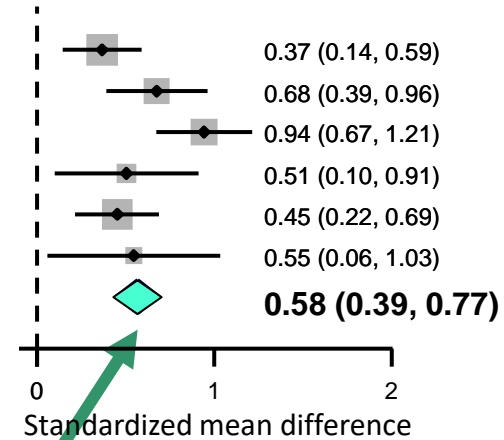
Using the **random effects model**:

There is not a single effect of haloperidol, but a whole distribution of effects with mean 0.58 and variance $\tau^2=0.009$

QTP vs PLA



HAL vs PLA



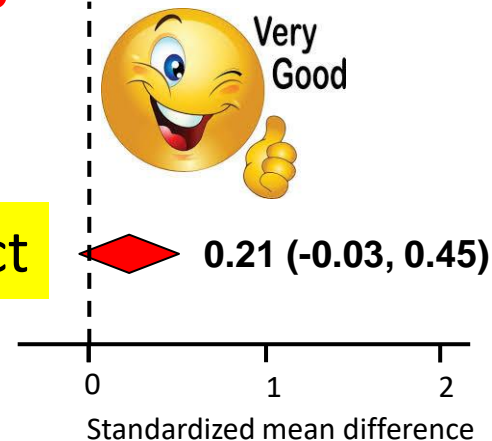
HAL is 0.58 better than P
QTP is 0.37 better than P

...so HAL is 0.21 better than QTP

but we need to combine the uncertainty
in both

Indirect

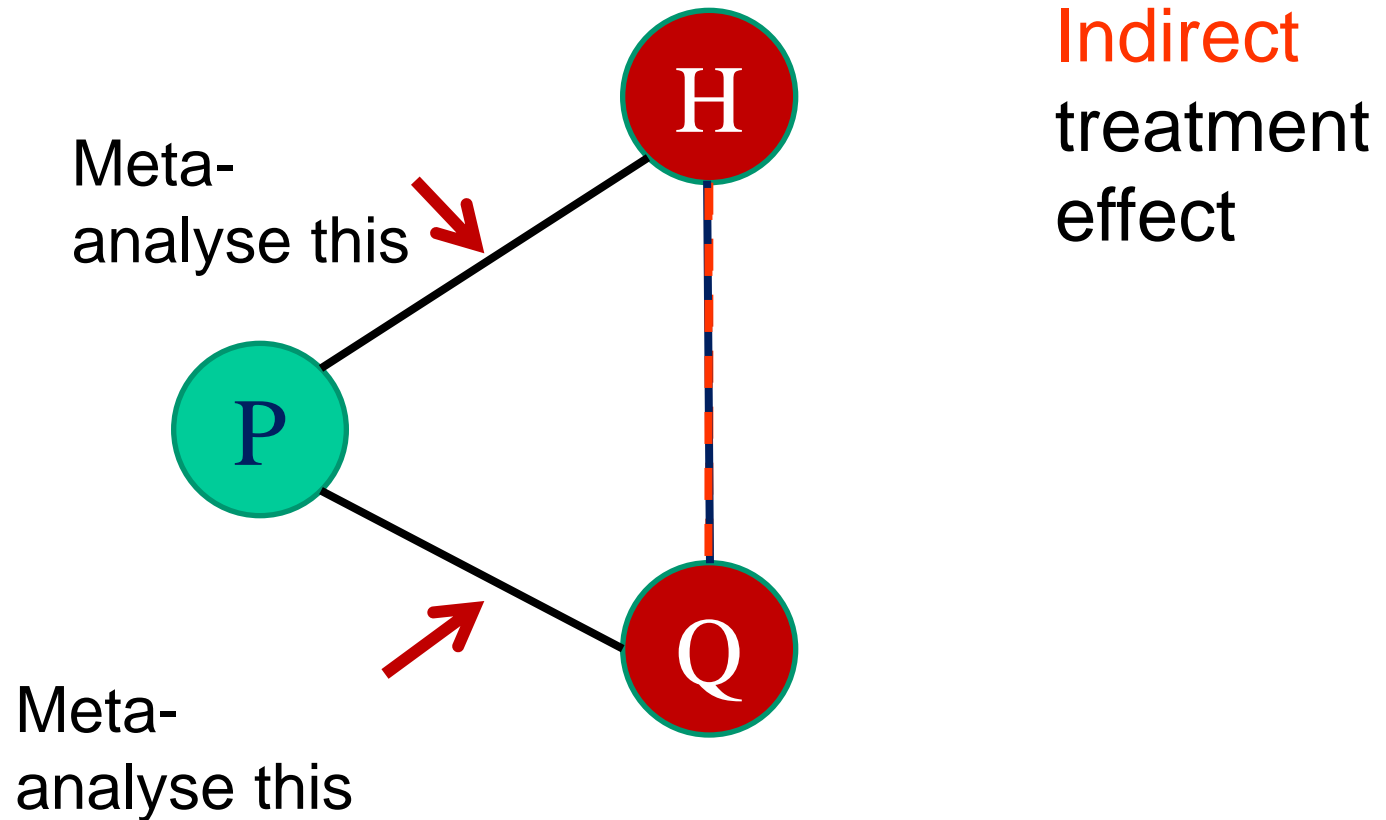
HAL vs QTP



Indirect comparison

$$\begin{aligned} &\text{advantage of HAL over QTP} = \\ &\quad \text{advantage of HAL over PLA} \\ &\quad - \\ &\quad \text{advantage of QTP over PLA} \end{aligned}$$

Indirect and mixed treatment effects



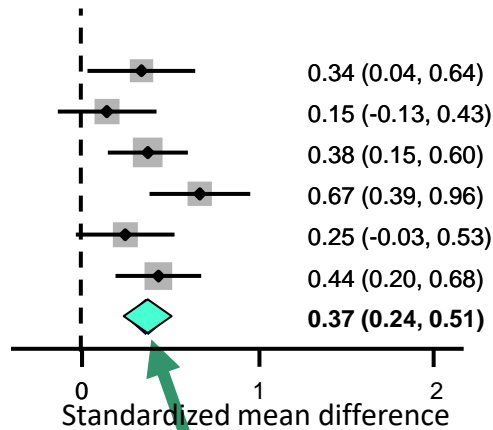
$$\text{SMD}_{\text{HQ}} = \text{SMD}_{\text{HP}} - \text{SMD}_{\text{QP}}$$

$$\text{Var}(\text{SMD}_{\text{HQ}}) = \text{Var}(\text{SMD}_{\text{HP}}) + \text{Var}(\text{SMD}_{\text{QP}})$$

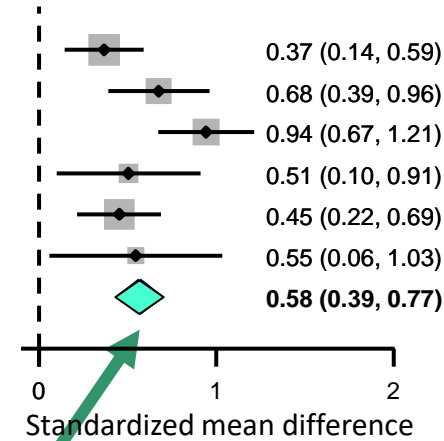
.... in the meanwhile

A new study was published!
It compares HAL and QTP!!!

QTP vs PLA



HAL vs PLA



HAL is 0.58 better than P

QTP is 0.37 better than P

...so HAL is 0.21 better than QTP

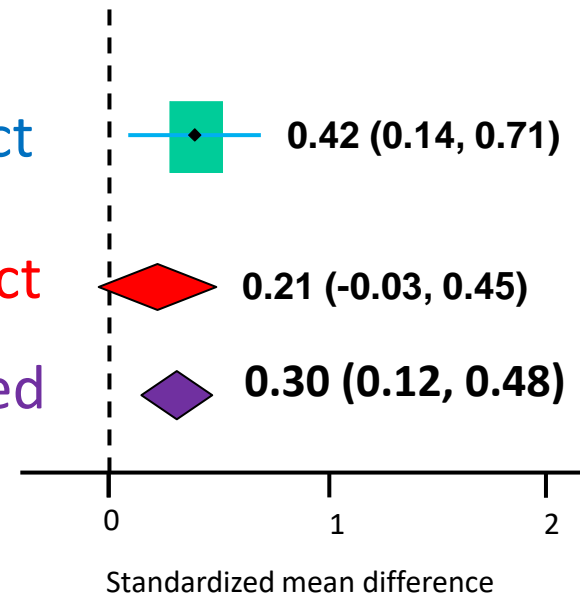
Synthesize **direct**
and **indirect**

Direct

Indirect

Mixed

HAL vs QTP



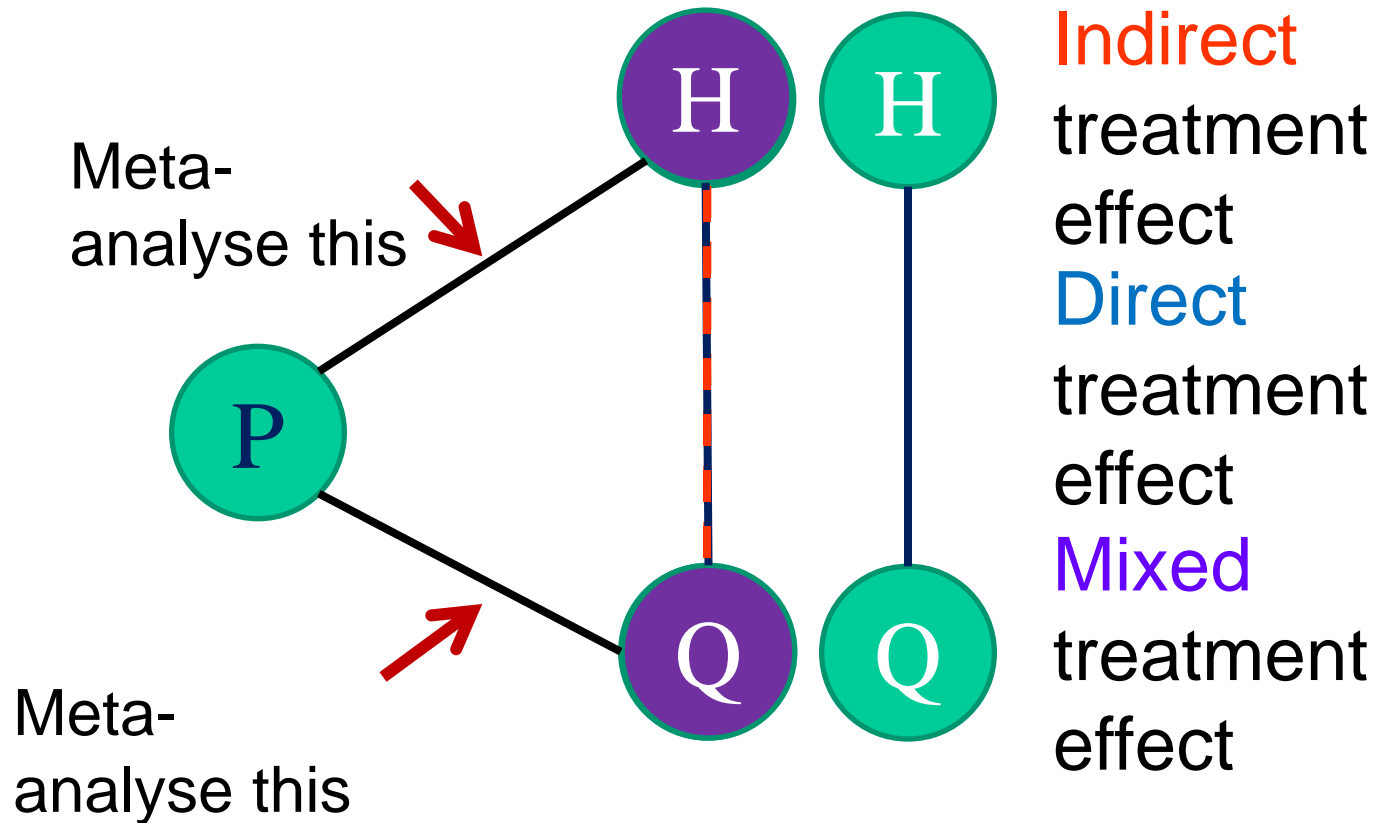
Mixed effect

Summarize **direct** and **indirect** effect size into a single **mixed** effect

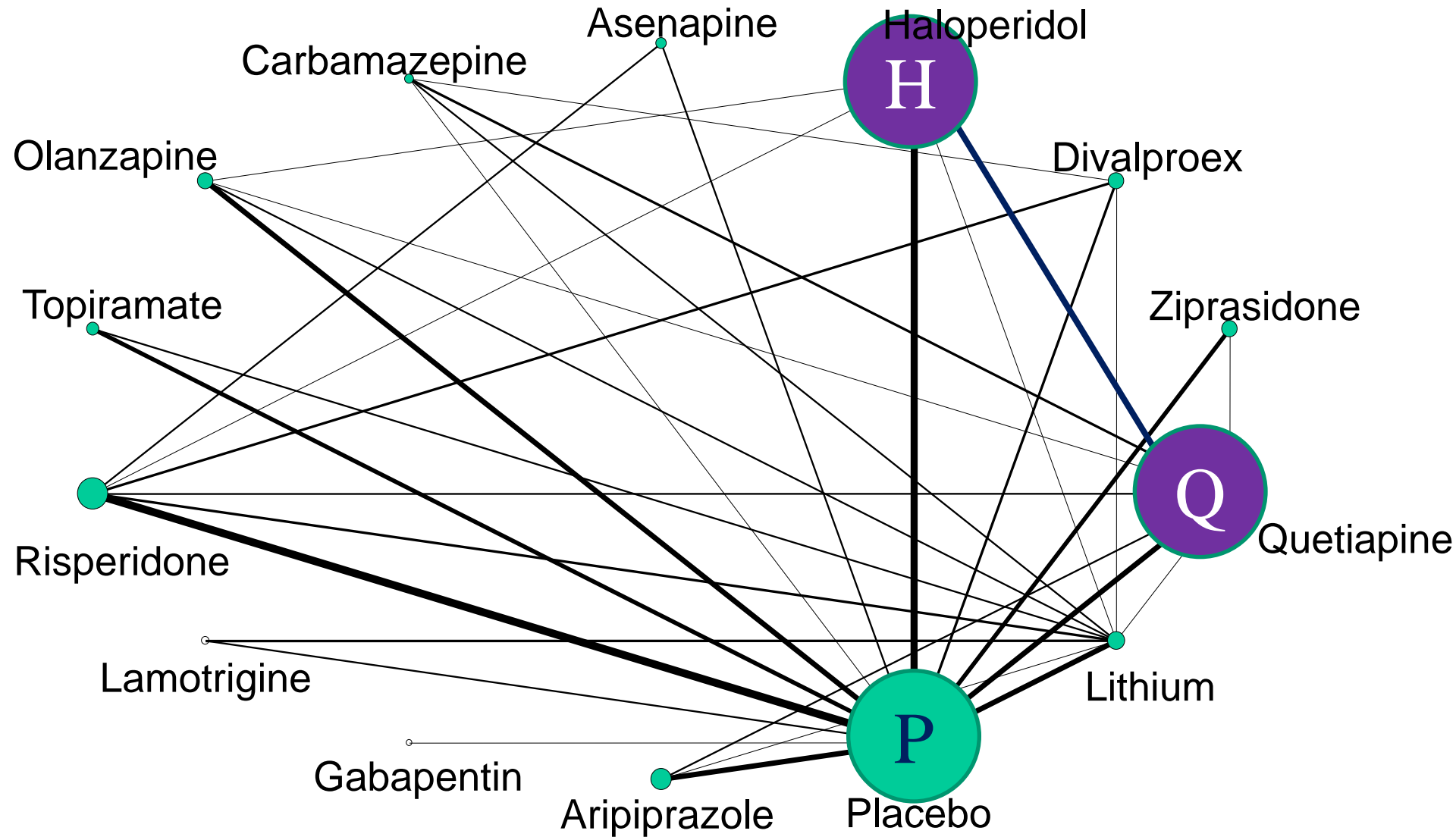
$$\text{mixed SMD} = \frac{\frac{SMD_{direct}}{\text{var}(SMD_{direct})} + \frac{SMD_{indirect}}{\text{var}(SMD_{indirect})}}{\frac{1}{\text{var}(SMD_{direct})} + \frac{1}{\text{var}(SMD_{indirect})}}$$

$$\text{var}(\text{mixed SMD}) = \frac{1}{\frac{1}{\text{var}(SMD_{direct})} + \frac{1}{\text{var}(SMD_{indirect})}}$$

Indirect and mixed treatment effects



Network of interventions for Acute Mania



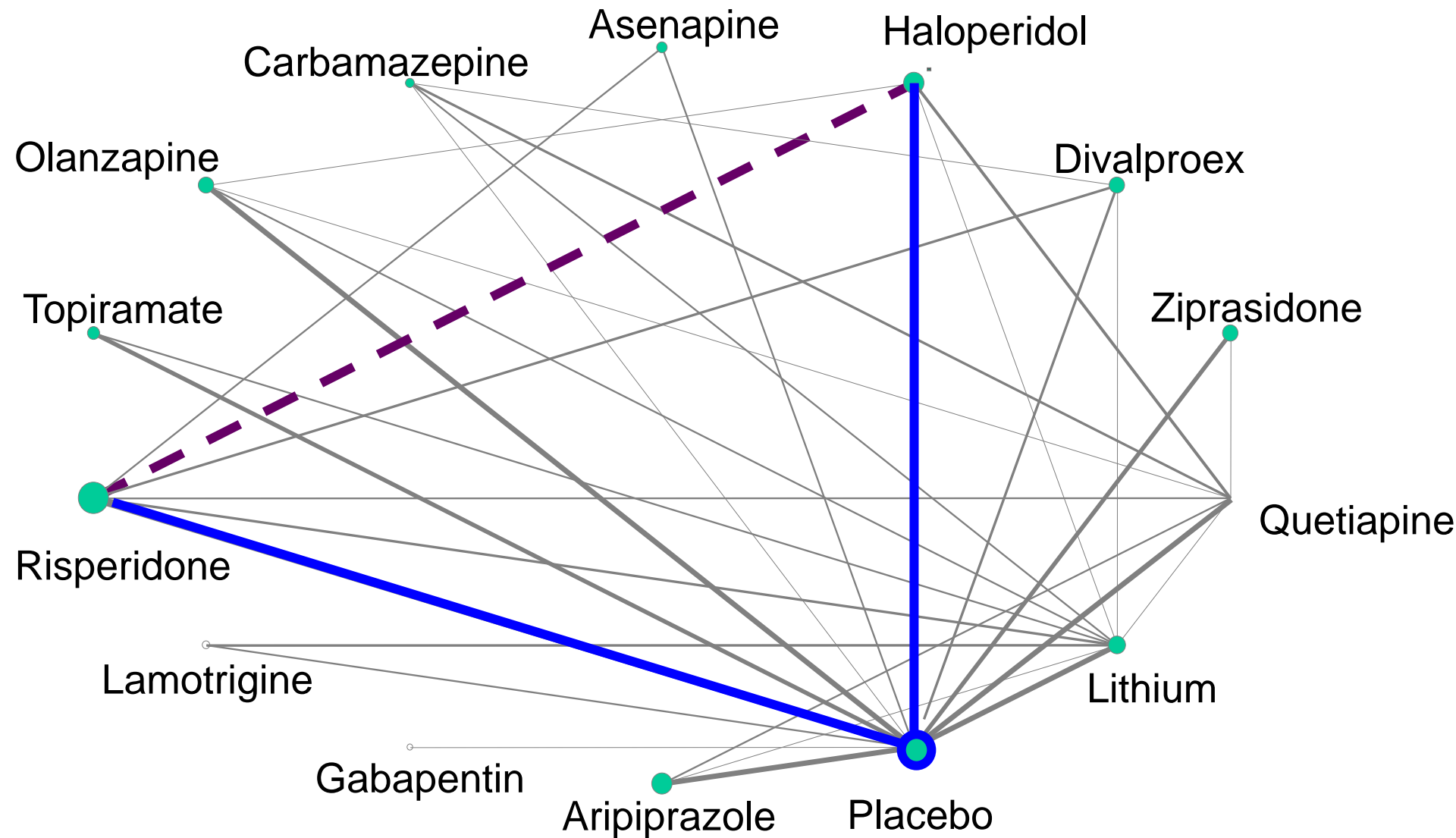
What if instead of this:



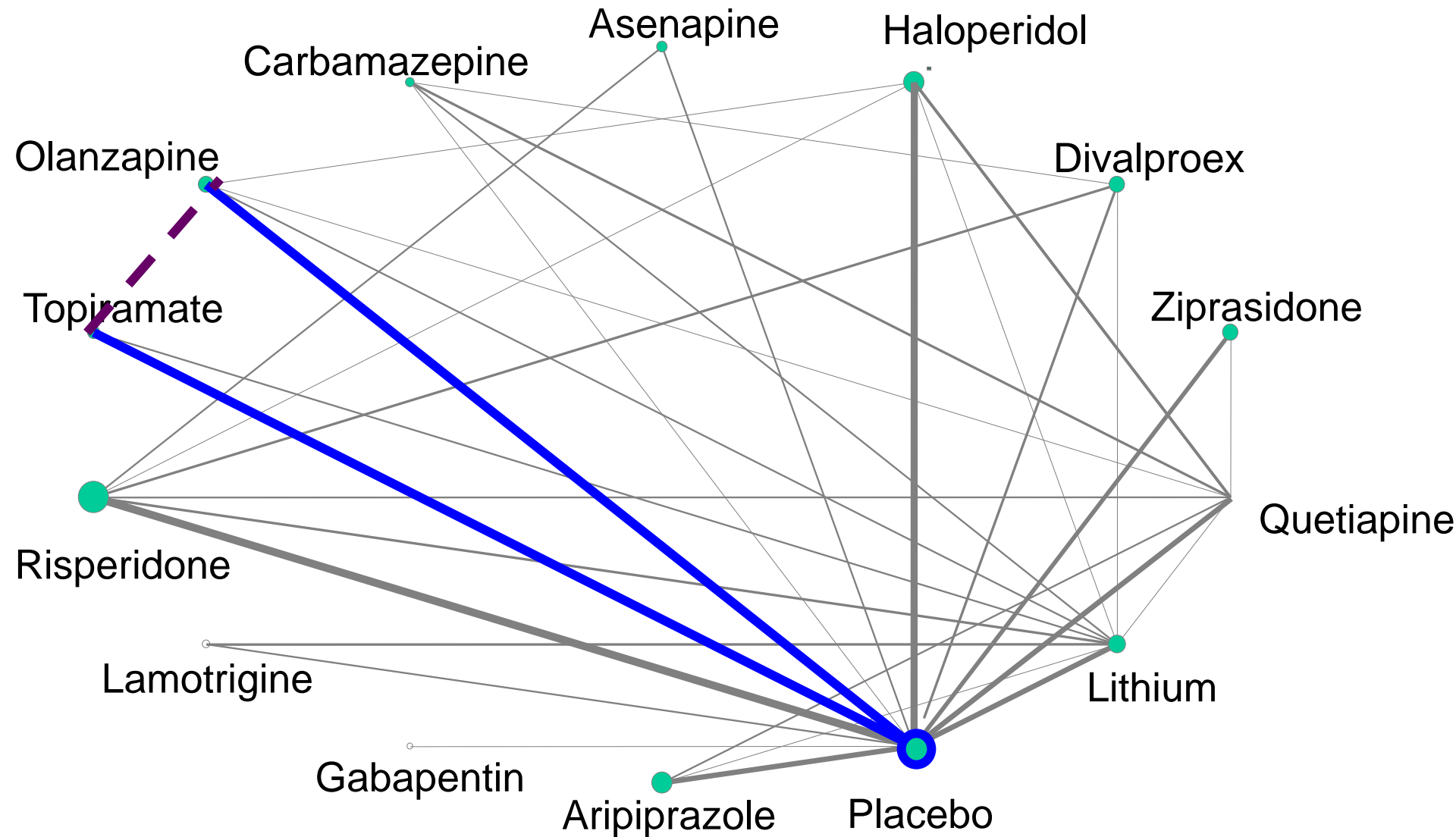
We have this:



Direct and Indirect evidence is synthesized in the entire network

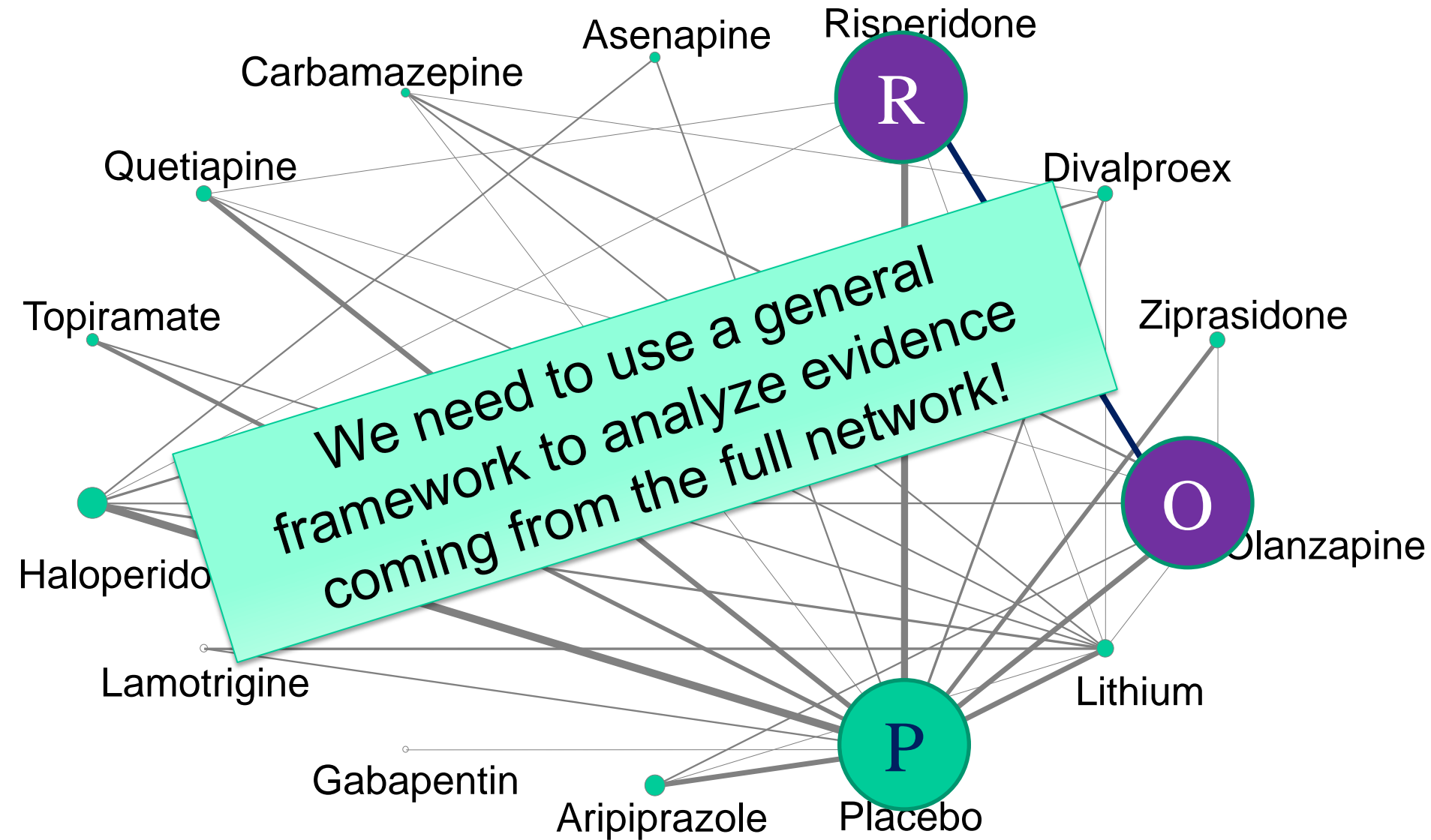


Direct and Indirect evidence is synthesized in the entire network



Comparative efficacy and acceptability of antimanic drugs. *Cipriani et al. Lancet* 2011

Network of interventions for Acute Mania



What network meta-analysis can do for you?

- Make the best use of all available evidence
- Avoid selective use of indirect evidence
- We compare interventions which haven't been directly compared in any experiment

SMD<0 favor the treatment in column

Direct relative treatment effects

| HAL | | | | | | | |
|-------------------------------|-------------------------------|-----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----|
| 0.02 (-0.17,0.21) | RIS | | | | | | |
| -0.15 (-0.32,0.03) | 0.04 (-0.18,0.25) | OLZ | | | | | |
| -1.11 (-1.89,0.33) | -0.67 (-1.40,0.07) | | LIT | | | | |
| -0.42 (-0.71,0.14) | -0.17 (-0.37,0.03) | -0.40 (-0.70,0.13) | 0.11 (-0.20,0.43) | QTP | | | |
| -0.05 (-0.20,0.10) | | | 0.06 (-0.16,0.28) | | ARI | | |
| 0.09 (-0.56,0.38) | | | -0.23 (-0.76,0.30) | | | CBZ | |
| <u>-0.58</u> (-0.77,-0.39) | <u>-0.50</u> (-0.67,-0.33) | | <u>-0.40</u> (-0.54,-0.26) | <u>-0.37</u> (-0.51,-0.24) | <u>-0.31</u> (-0.42,-0.20) | <u>-0.50</u> (-0.69,-0.30) | PBO |

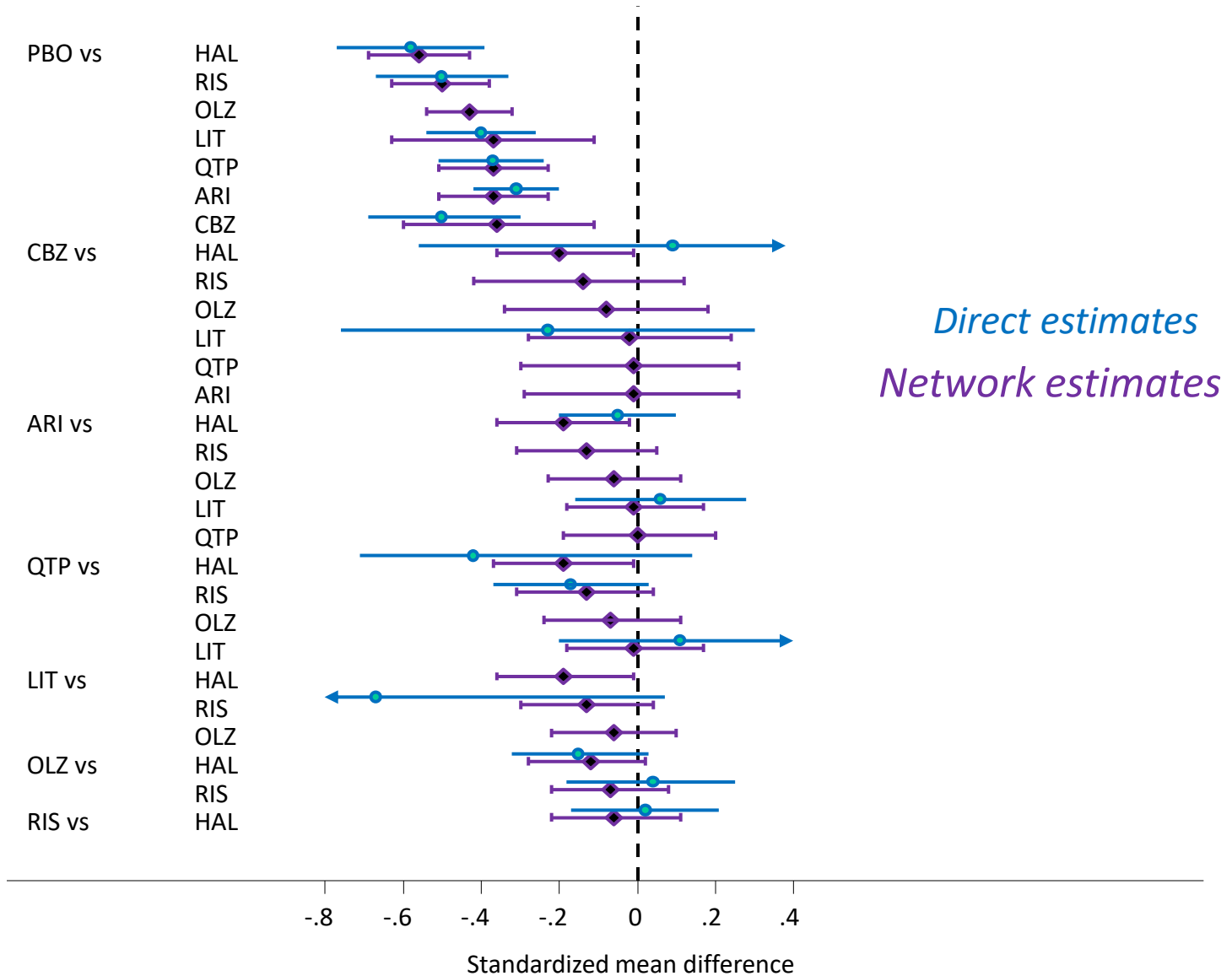
NMA relative treatment effects

| HAL | | | | | | | |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----|
| -0.06 (-0.22,0.11) | RIS | | | | | | |
| -0.12 (-0.28,0.02) | -0.07 (-0.22,0.08) | OLZ | | | | | |
| <u>-0.19</u> (-0.36,-0.01) | -0.13 (-0.30,0.04) | -0.06 (-0.22,0.10) | LIT | | | | |
| <u>-0.19</u> (-0.37,-0.01) | -0.13 (-0.31,0.04) | -0.07 (-0.24,0.11) | -0.01 (-0.18,0.17) | QTP | | | |
| <u>-0.19</u> (-0.36,-0.02) | -0.13 (-0.31,0.05) | -0.06 (-0.23,0.11) | -0.01 (-0.18,0.17) | 0.00 (-0.19,0.20) | ARI | | |
| <u>-0.20</u> (-0.36,-0.01) | -0.14 (-0.42,0.12) | -0.08 (-0.34,0.18) | -0.02 (-0.28,0.24) | -0.01 (-0.30,0.26) | -0.01 (-0.29,0.26) | CBZ | |
| <u>-0.56</u> (-0.69,-0.43) | <u>-0.50</u> (-0.63,-0.38) | <u>-0.43</u> (-0.54,-0.32) | <u>-0.37</u> (-0.63,-0.11) | <u>-0.37</u> (-0.51,-0.23) | <u>-0.37</u> (-0.51,-0.23) | <u>-0.36</u> (-0.60,-0.11) | PBO |

What network meta-analysis can do for you?

- Make the best use of all available evidence
- Avoid selective use of indirect evidence
- We compare interventions which haven't been directly compared in any experiment
- It can increase precision in the estimations

Precision is gained!



What network meta-analysis can do for you?

- Make the best use of all available evidence
- Avoid selective use of indirect evidence
- We compare interventions which haven't been directly compared in any experiment
- It can increase precision in the estimations
- It can rank all competing treatments and hence it can answer policy-relevant questions

Network meta-analysis

key messages

Network meta-analysis is an extension of traditional, pairwise meta-analysis

Network meta-analysis synthesises both **direct and indirect evidence** in a network of trials that contain multiple interventions

Network meta-analysis facilitates “all way” comparisons, and generates relative effect estimates between any two interventions and ranking probabilities for interventions

Network meta-analysis can give valuable insight into the **comparative benefits and harms** of multiple alternative treatment options