Methods for network meta-analysis and ranking of treatments

Anna Chaimani

Research Center of Epidemiology and Statistics Sorbonne Paris Cité (CRESS-UMR1153), Inserm, Université de Paris

Service de Biostatistique et d'Epidémiologie de Gustave Roussy

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Meta-analysis in the literature

- Systematic reviews and meta-analyses of randomized controlled trials have "*transformed medicine*"
  - Establish evidence-based practice
  - Resolve contradictory research outcomes
  - Support research planning and prioritization

- Massive production of meta-analyses assessing healthcare interventions
  - More than 10,000 meta-analyses of RCTs per year

Donnelly et al., ***Nature*** *2018*
Sutherland et al. ***Nature*** *2018*

Limitation of pairwise meta-analysis

Example: Antidepressants for major depression

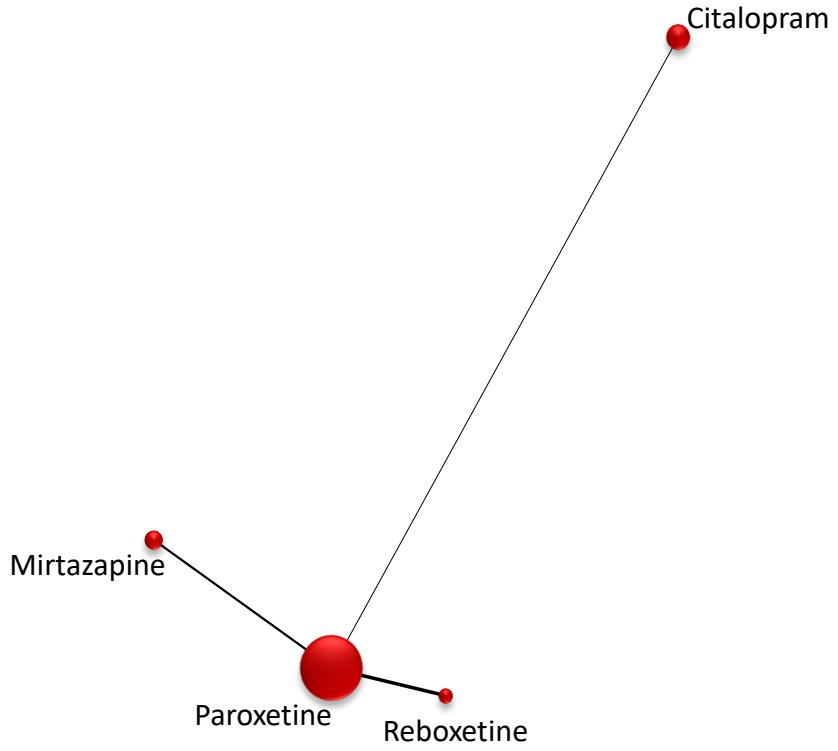
Paroxetine versus other anti-depressive agents for depression

Marianna Purgato[1], Davide Papola[1], Chiara Gastaldon[1], Carlotta Trespidi[1], Laura R Magni[2], Carla Rizzo[3], Toshi A Furukawa[4], Norio Watanabe[5], Andrea Cipriani[6], Corrado Barbui[1]

"Paroxetine was more effective than reboxetine…"

"…less effective than mirtazapine"

"…less effective than citalopram"



Purgato et al. ***Cochrane Database Syst Rev*** *2014*

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Example: Antidepressants for major depression

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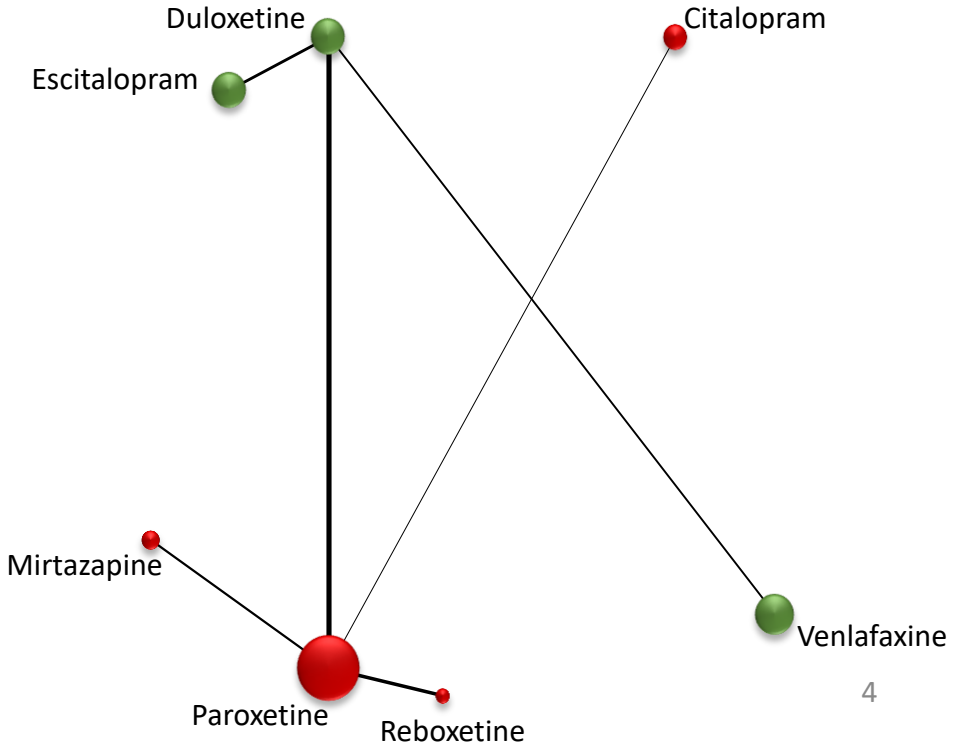
Duloxetine versus other anti-depressive agents for depression

Andrea Cipriani[1], Markus Koesters[2], Toshi A Furukawa[3], Michela Nosè[4], Marianna Purgato[1], Ichiro M Omori[5], Carlotta Trespidi[1], Corrado Barbui[1]

"…no statistically significant differences in efficacy when compared with other antidepressants…"

"…when compared with escitalopram or venlafaxine, there was a higher drop-out rate…"

"…more adverse events than paroxetine…"



Cipriani et al. ***Cochrane Database Syst Rev*** *2012*

From pairwise to network meta-analysis

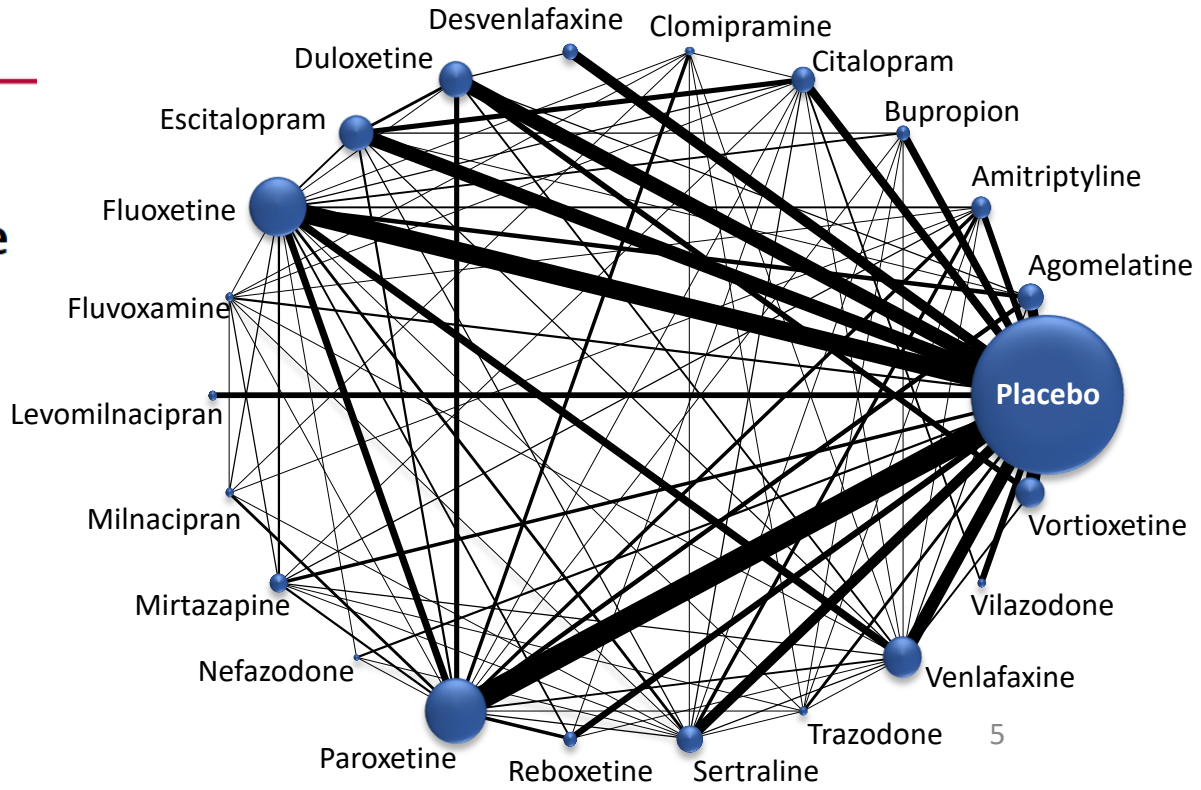
Example: Antidepressants for major depression

The most critical question raised by patients and clinicians at the point of care is

"what is the drug of choice for the given condition?"

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

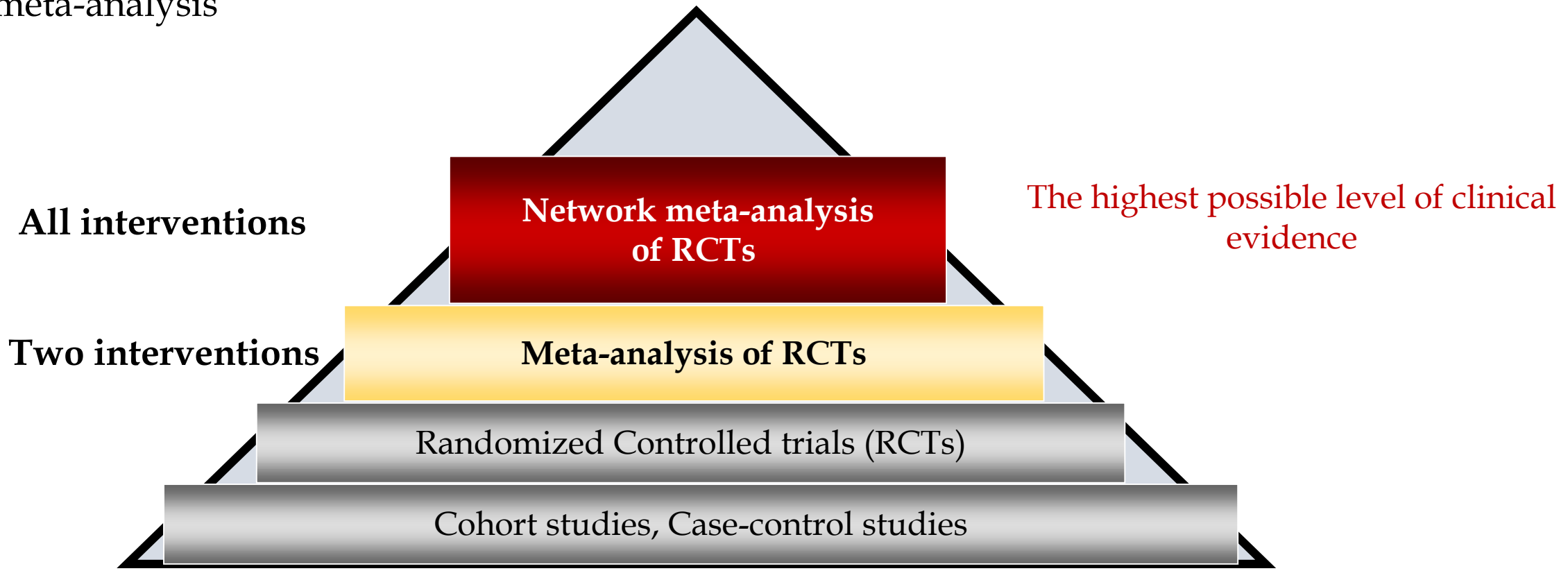
Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*



Cipriani et al. ***Lancet*** *2018*

Network meta-analysis in medical research

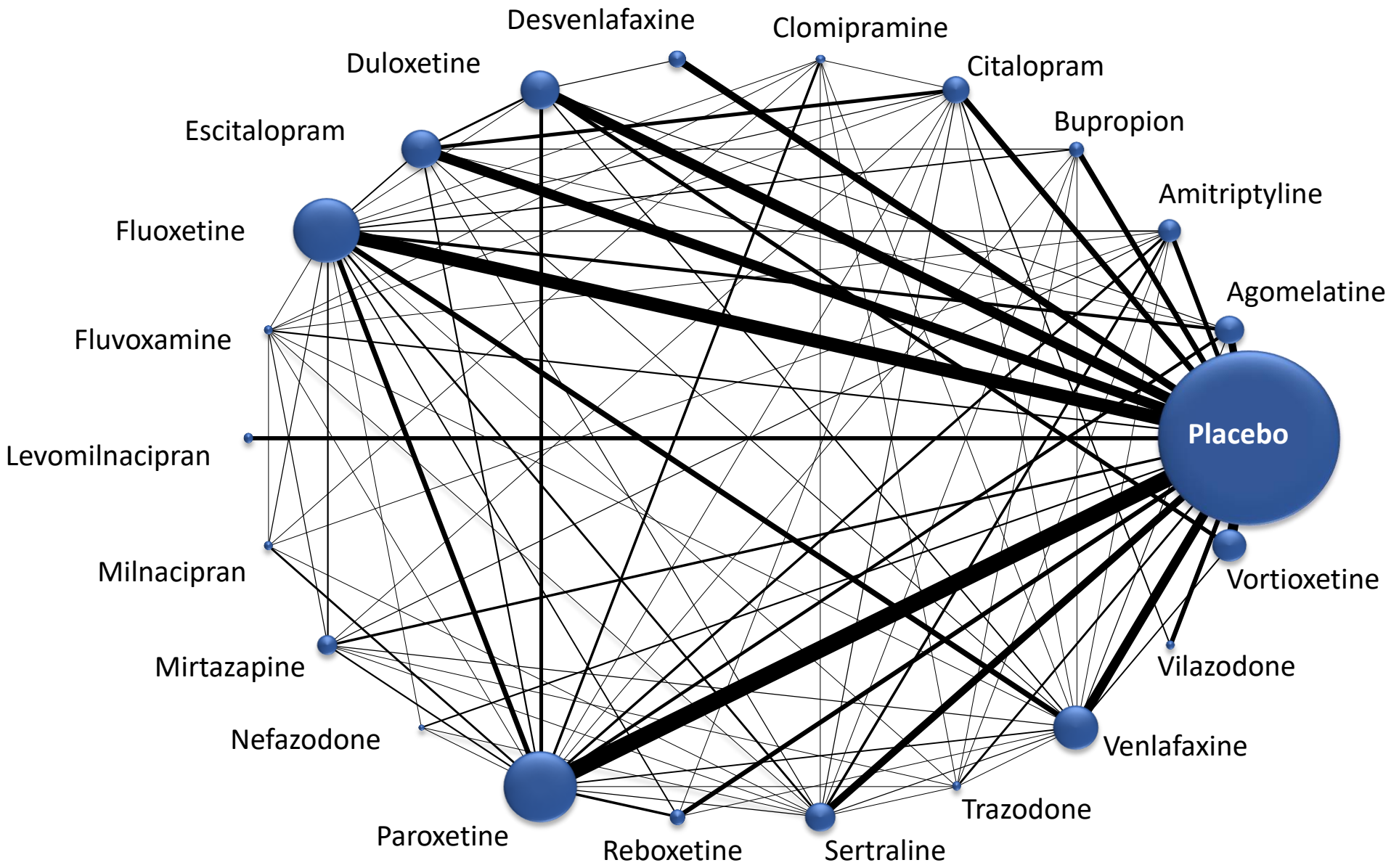
WHO (World Health Organization) guidelines now rely whenever possible on network meta-analysis



The highest possible level of clinical evidence

Faltinsen et al. ***BMJ Evid Based Med*** *2018*
Leucht et al. ***Eur Arch Psychiatry Clin Neurosci*** *2016*

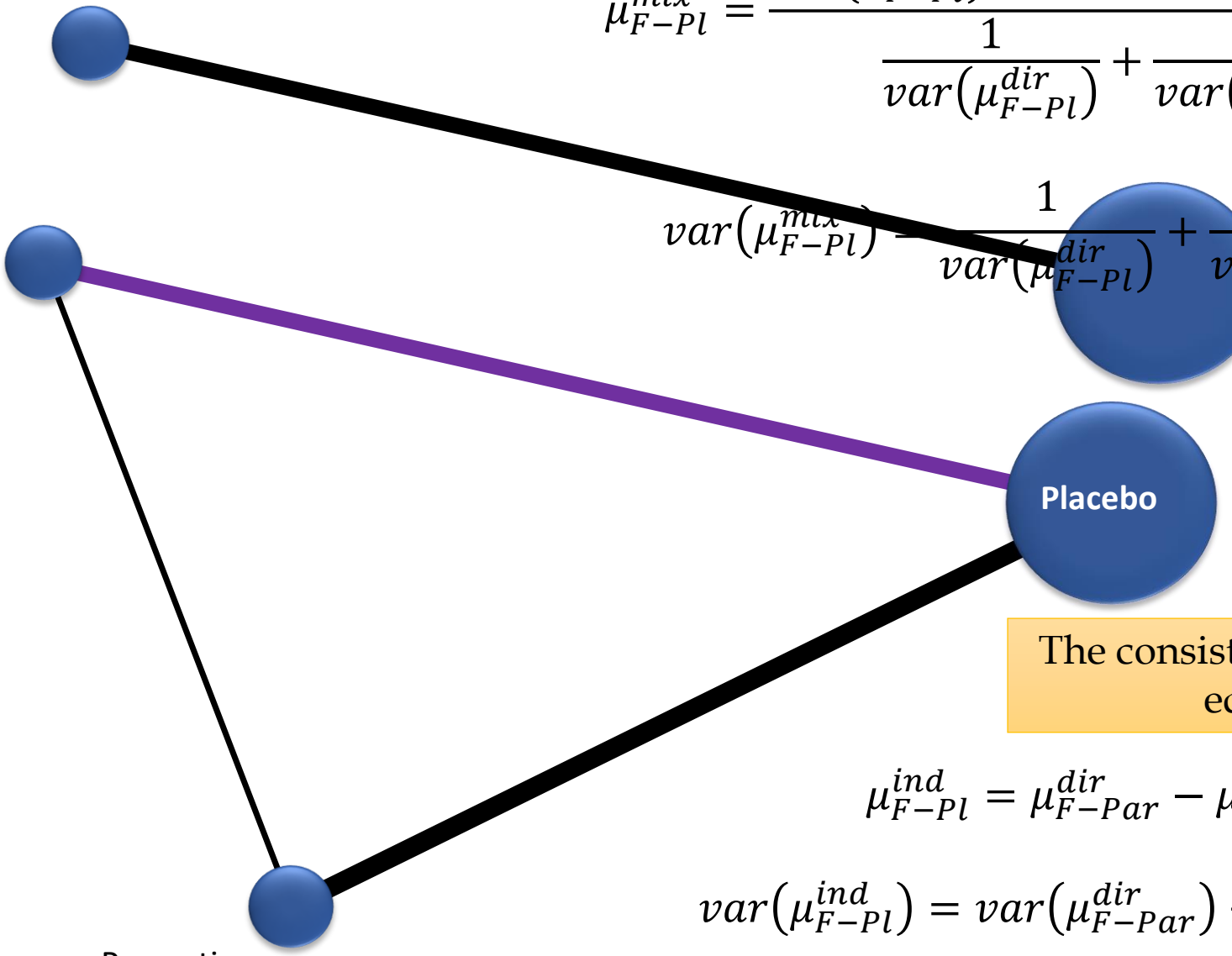
Indirect and mixed effects



Indirect and mixed effects

$$\mu_{F-Pl}^{mix} = \frac{\frac{1}{var(\mu_{F-Pl}^{dir})}\mu_{F-Pl}^{dir} - \frac{1}{var(\mu_{F-Pl}^{ind})}\mu_{F-Pl}^{ind}}{\frac{1}{var(\mu_{F-Pl}^{dir})} + \frac{1}{var(\mu_{F-Pl}^{ind})}}$$

$$var(\mu_{F-Pl}^{mix}) = \frac{1}{var(\mu_{F-Pl}^{dir})} + \frac{1}{var(\mu_{F-Pl}^{ind})}$$



Indirect effect

Direct effect

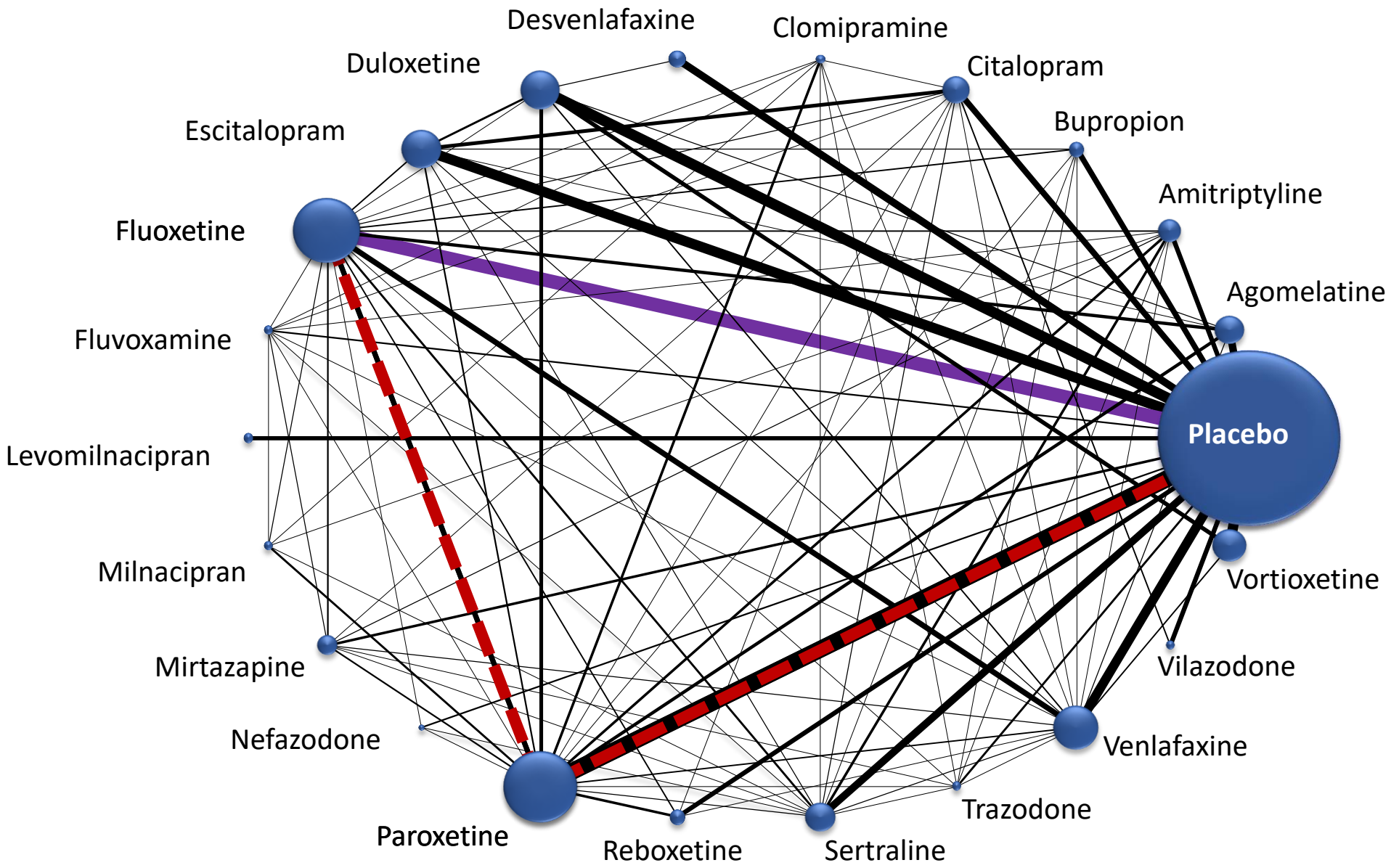
Mixed effect

The consistency/coherence equation

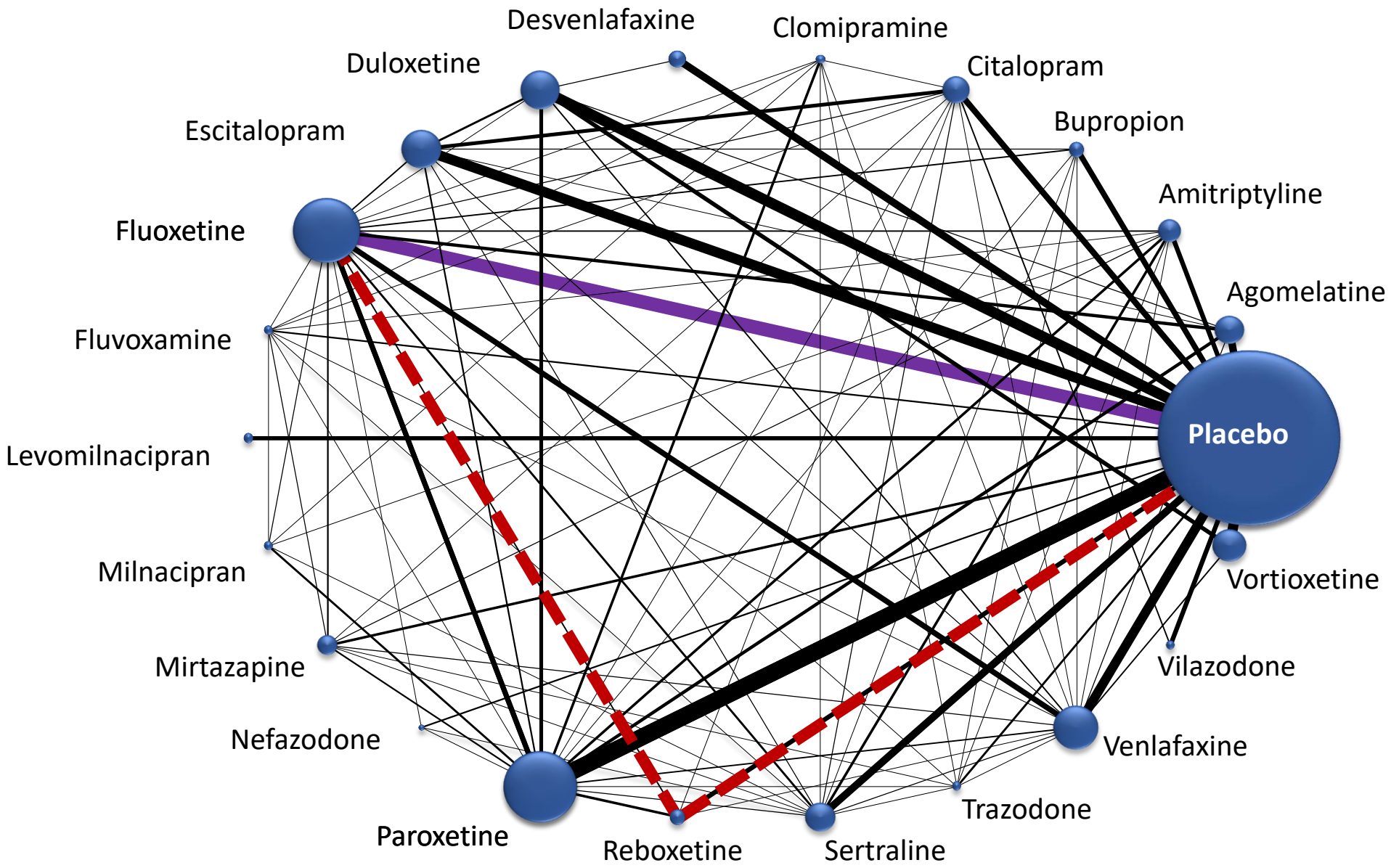
$$\mu_{F-Pl}^{ind} = \mu_{F-Par}^{dir} - \mu_{Pl-Par}^{dir}$$

$$var(\mu_{F-Pl}^{ind}) = var(\mu_{F-Par}^{dir}) + var(\mu_{Pl-Par}^{dir})$$

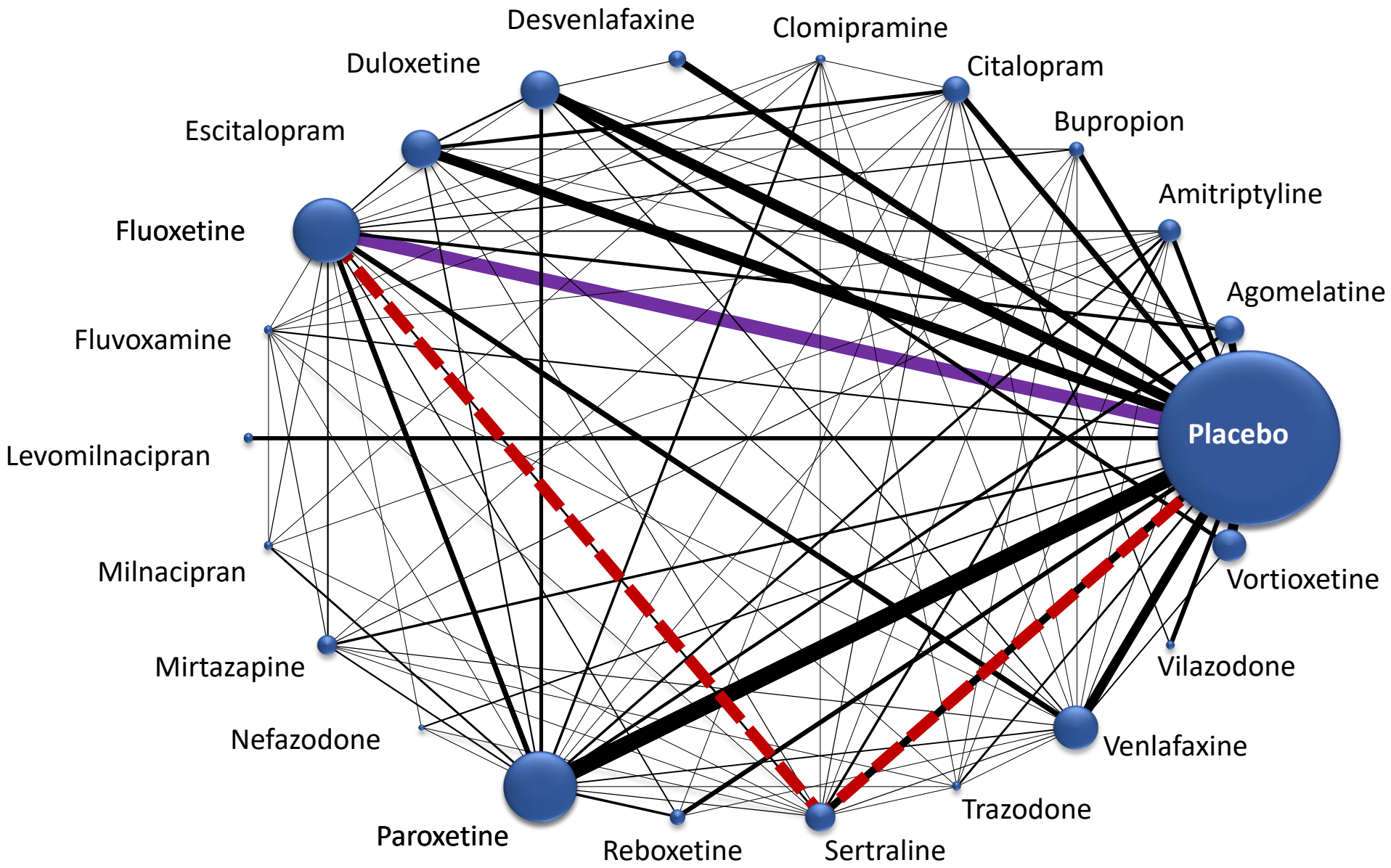
Indirect and mixed effects



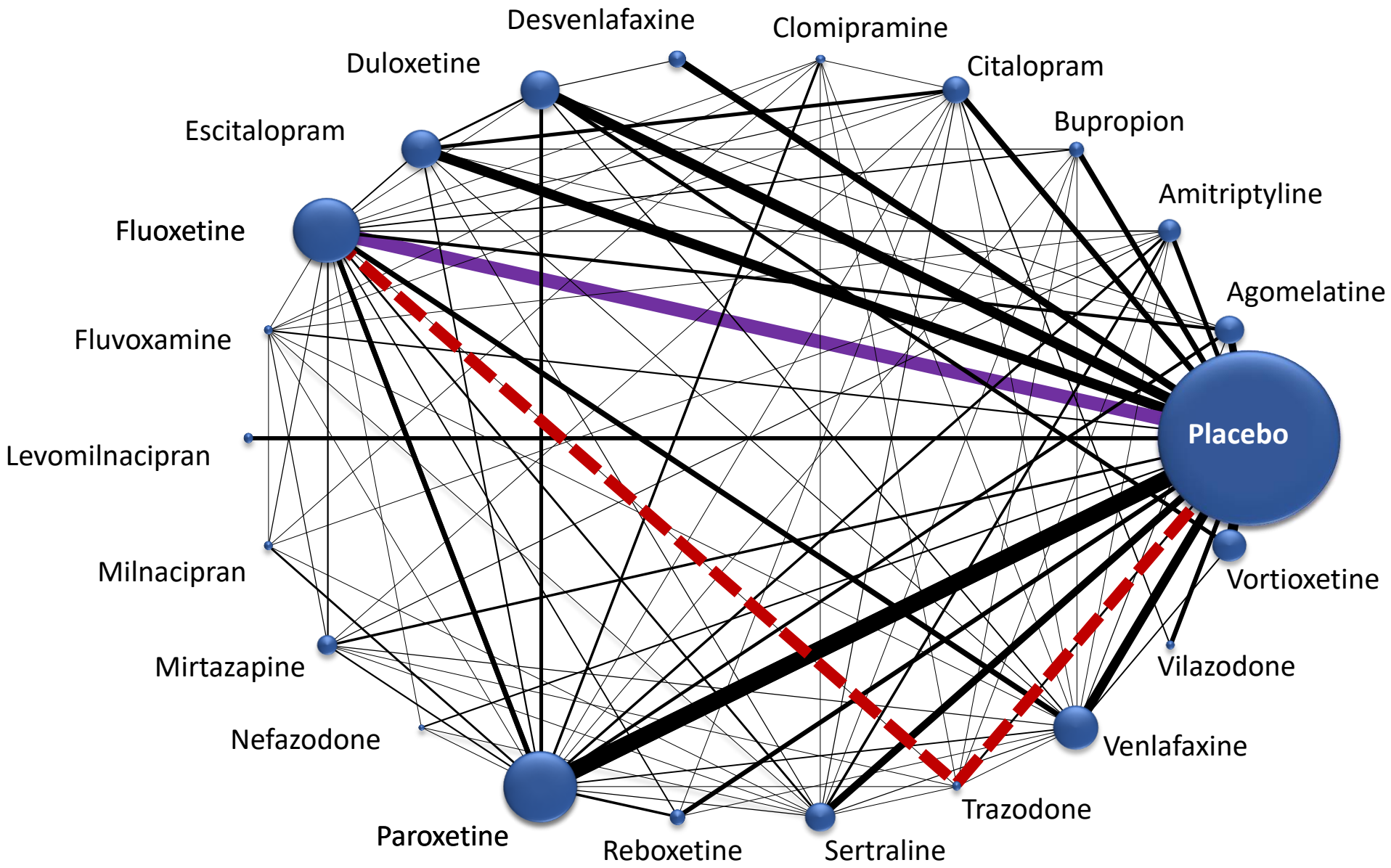
Indirect and mixed effects



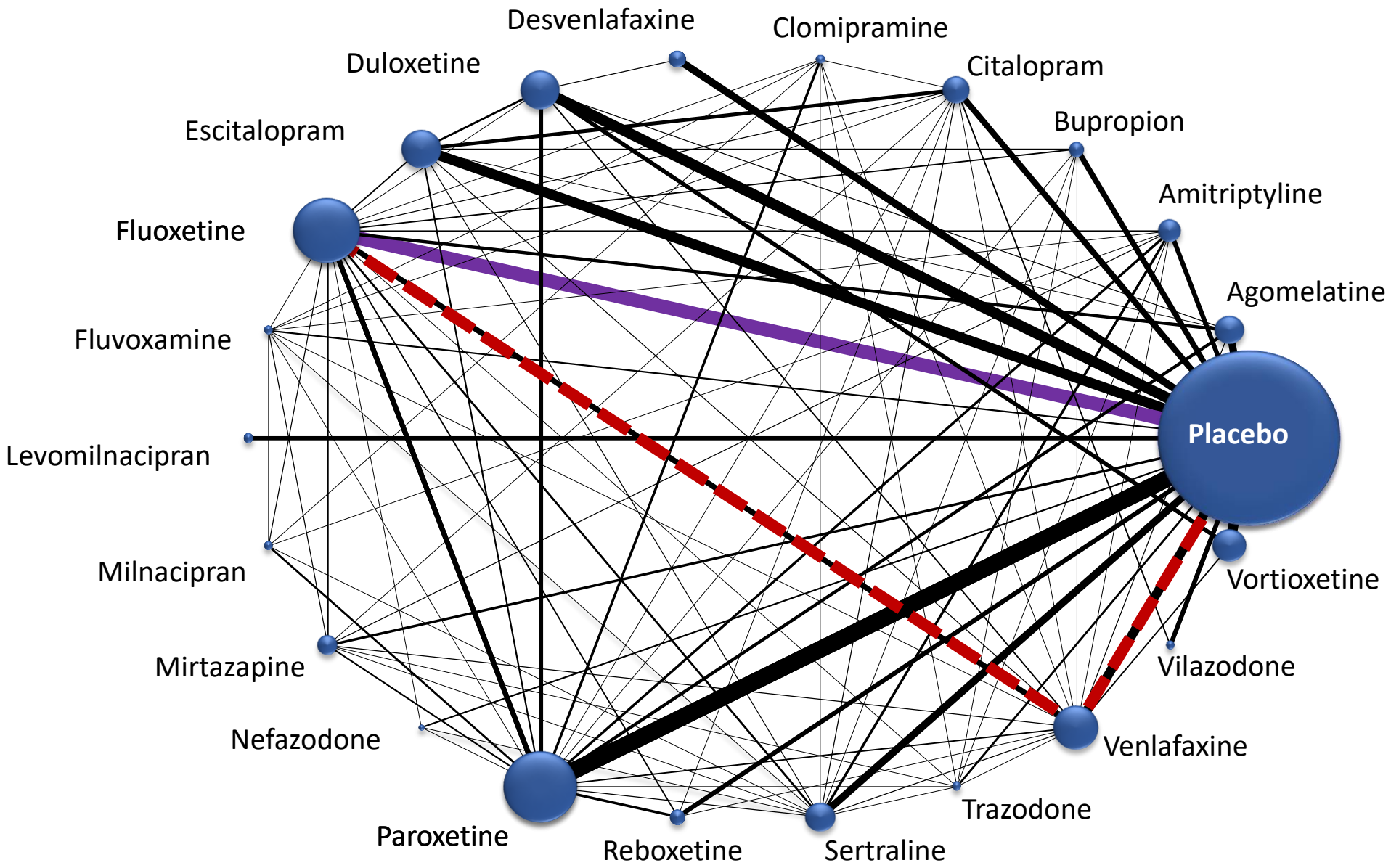
Indirect and mixed effects



Indirect and mixed effects



Indirect and mixed effects



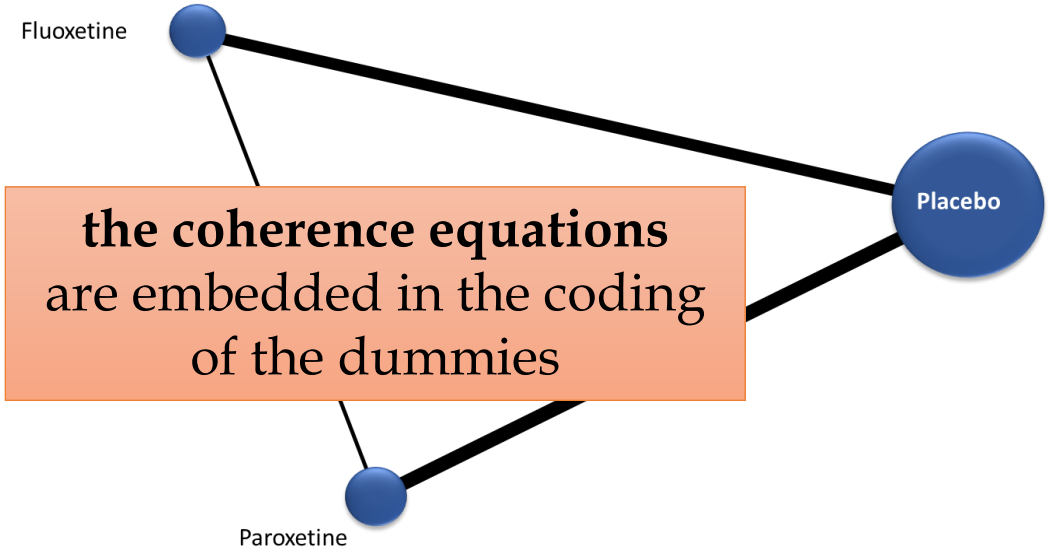
Overview of approaches to network meta-analysis

- Simple meta-regression (any software)
- Multivariate meta-analysis (Stata – network package)
- Multivariate meta-regression (Stata – network package)
- Hierarchical model (Bayesian software – BUGS, JAGS)
- Electrical networks and graph theory (R – netmeta package)

Network meta-analysis as meta-regression

$$y_i = \beta_1 \, x_i^{F-Pl} + \beta_2 \, x_i^{Par-Pl} + \delta_i + \varepsilon_i$$

Trial	Comparison	x_i^{F-Pl}	x_i^{Par-Pl}
1	Fluo vs Pla	1	0
2	Fluo vs Pla	1	0
3	Paro vs Pla	0	1
4	Paro vs Pla	0	1
5	Paro vs Pla	0	1
6	Fluo vs Paro	1	-1
7	Fluo vs Paro	1	-1
.	.	.	.
.	.	.	.
.	.	.	.



the coherence equations are embedded in the coding of the dummies

Placebo is used as the **reference**.

Meta-regression on these data will give

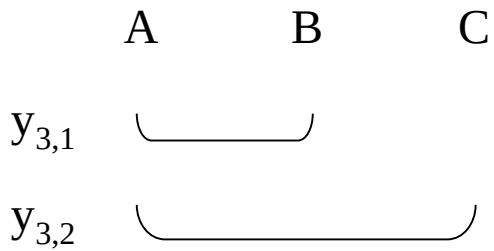
- Fluo vs Pla (mixed): β_1
- Paro vs Pla (mixed): β_2
- Fluo vs Paro (mixed): $\beta_1 - \beta_2$

Lumley ***Stat Med*** *2002*

Network meta-analysis as meta-regression

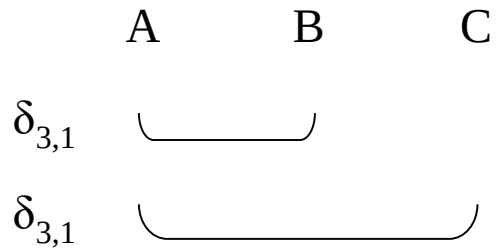
Multi-arm trials

- If we model treatment effect estimates, these are correlated if they include the same treatment (hence same patients)



- In random-effects network meta-analyses, treatment effect parameters are also correlated when they come from the same study

The **multivariate meta-regression** approach accounts for this correlation



Network meta-analysis as multivariate meta-analysis

- In multivariate meta-analysis we synthesize multiple outcomes
- What if we treat the different comparisons as different outcomes?

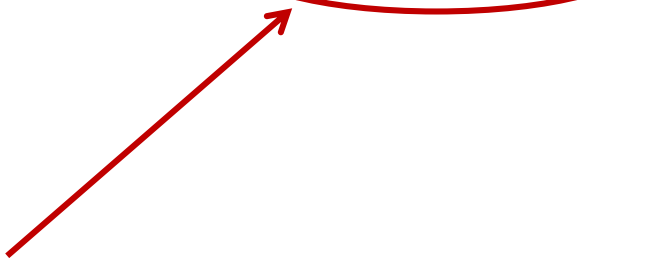
Study	No. arms	#Comparisons	Data	Outcome
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	systolic
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	diastolic
i=3	T_3=3	2	$y_{3,1}$, $v_{3,1}$ $y_{3,2}$, $v_{3,2}$ cov($y_{3,1}$, $y_{3,2}$)	systolic diastolic

White et al. ***Res Synth Meth*** *2012*

Network meta-analysis as multivariate meta-analysis

Simple example

Study	No. arms	No. effects	Data	Contrast
i=1	$T_1=2$	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	$T_2=2$	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	$T_3=3$	2	$y_{3,1}$, $v_{3,1}$ $y_{3,2}$, $v_{3,2}$ $\text{cov}(y_{3,1}, y_{3,2})$	AB AC



we introduce their covariance

Network meta-analysis as multivariate meta-analysis

Simple example

Study	No. arms	No. effects	Data	Contrast
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	T_3=3	2	$y_{3,1}$, $v_{3,1}$ $y_{3,2}$, $v_{3,2}$ cov($y_{3,1}$, $y_{3,2}$)	AB AC
i=4	T_4=3	2	$y_{4,1}$, $v_{4,1}$	**BC**

How to model a study that reports BC?

Network meta-analysis as multivariate meta-analysis

Simple example

Study	No. arms	No. effects	Data	Contrast
i=1	T_1=2	1	$y_{1,1}$, $v_{1,1}$	AB
i=2	T_2=2	1	$y_{2,1}$, $v_{2,1}$	AC
i=3	T_3=3	2	$y_{3,1}$, $v_{3,1}$ $y_{3,2}$, $v_{3,2}$ cov($y_{3,1}$, $y_{3,2}$)	AB AC
i=4	T_4=3	2	$y_{4,1}$, $v_{4,1}$ $y_{4,2}$, $v_{4,2}$ cov($y_{4,1}$, $y_{4,2}$)	AB AC

'Impute' minimal information

We assume all studies include treatment A

When some trials don't include arm A, we "augment" the observed data

we create an arm A with a very small amount of data

e.g. 0.01 individuals with 10% success

Adding a near-empty arm A to a trial B vs C yields treatment effects B vs A and C vs A with very large standard errors large covariance – so that the data still convey the evidence about B vs C

Network meta-analysis using electrical networks and graph theory

Rücker ***Res Synth Meth*** *2012*

Meta-analytic network		Electrical network
Treatments	⇔	Nodes
Observed comparisons	⇔	Edges
Variance V of a comparison	⇔	Resistance R of an edge
Inverse variance weight $w = 1/V$	⇔	Conductance $1/R$
Treatment response in an arm	⇔	Potential at a node
Treatment effect for a comparison	⇔	Voltage at an edge
Weighted treatment effect	⇔	Current flow

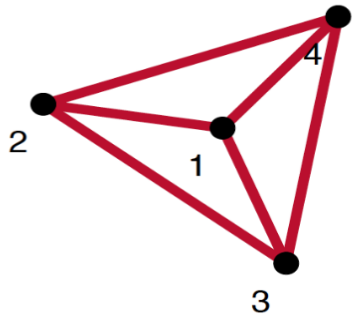
- Variances combine like electrical resistances [Bailey, 2007]
- Ohm's law relates treatment effects and weights
- Kirchhoff's current law says how to combine the observed effects
- Kirchhoff's potential law guarantees coherence of the estimated treatment effects over closed loops
  - Coherence means that the difference between two treatments is always the same, whatever (direct or indirect) path is chosen – the coherence assumption

Network meta-analysis using electrical networks and graph theory

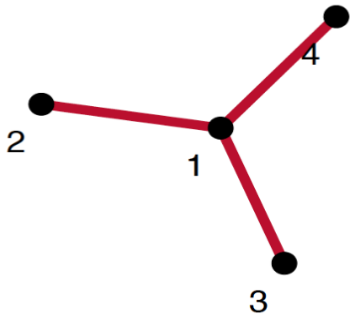
Multi-arm trials

- Similar to (multivariate) meta-regression (with dummy covariates, design matrix)
- Adjustment for multi-arm studies is done by reducing the weights of all comparisons (Rücker, 2012; Rücker and Schwarzer, 2014)

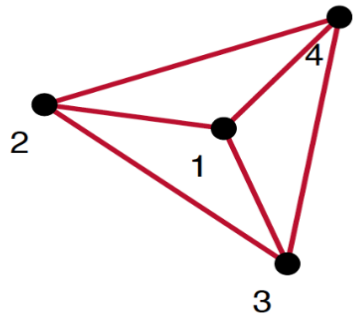
Given a four-arm study with six comparisons,



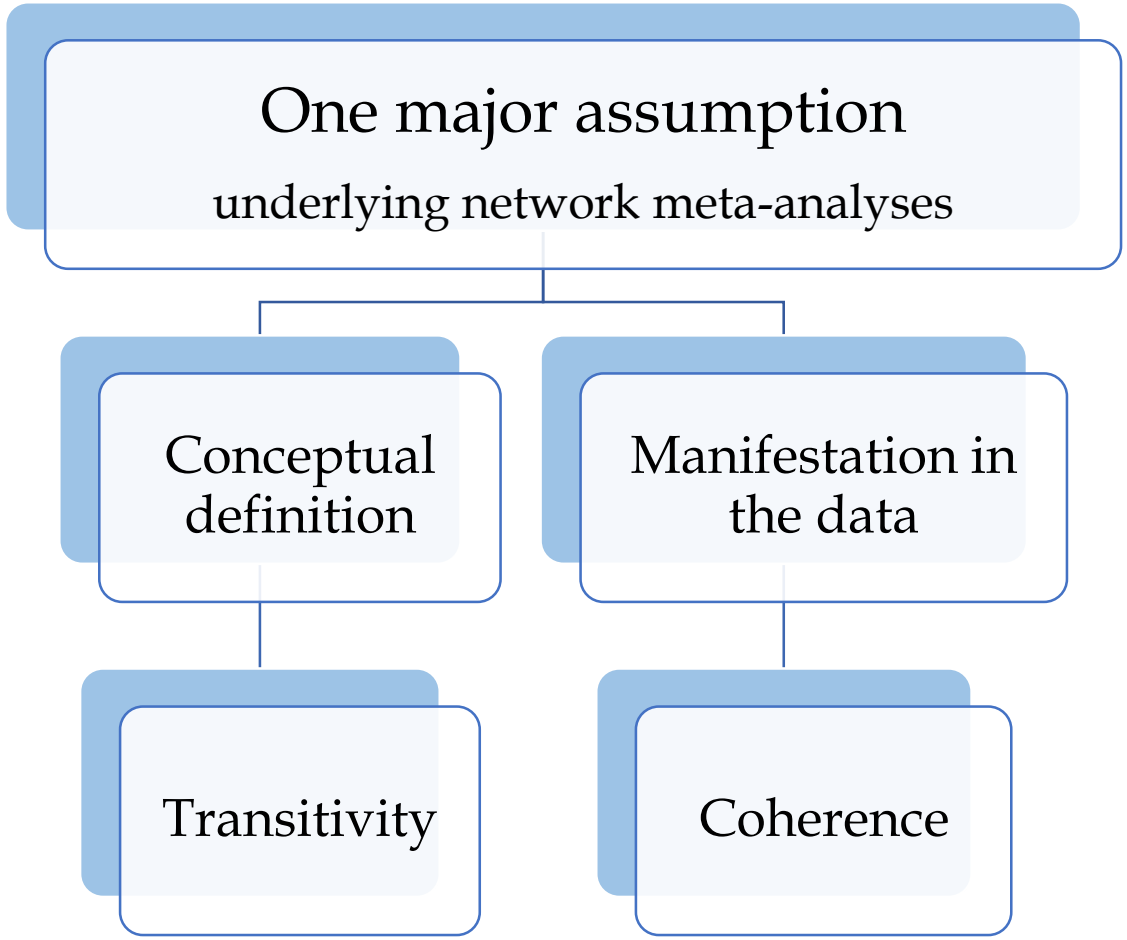
we may cut off three of six comparisons:



or reduce all weights by 1/2 (on average):

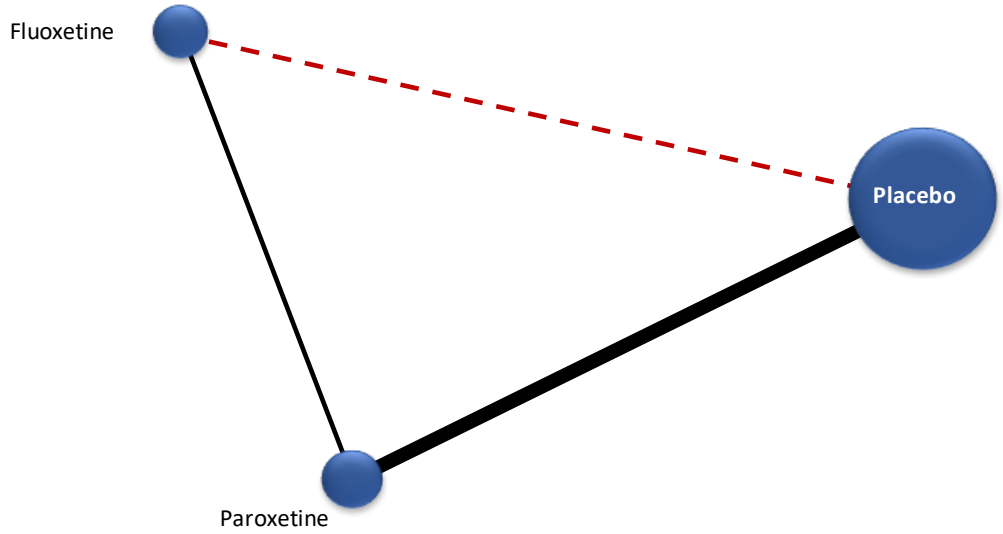


Assumptions of network meta-analysis



Transitivity

The underlying assumption when B versus C is calculated *indirectly* is that we can learn about B versus C via A.

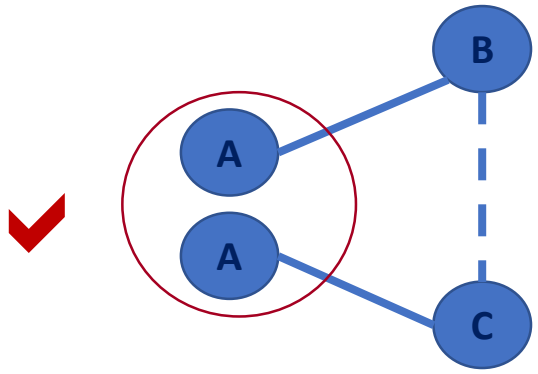


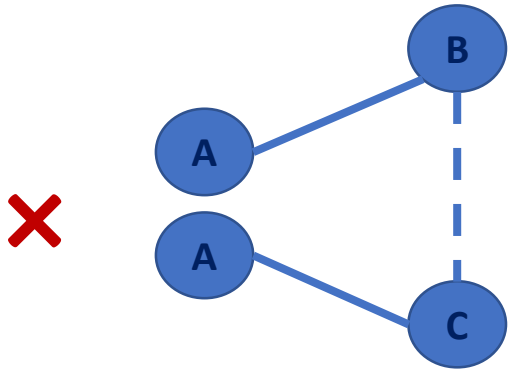
Validity depends on **transitivity** of treatment effects across trials making different treatment comparisons

advantage of B over C =
advantage of B over A + advantage of A over C

Requires studies to be similar in ways other than the treatments being compared

Ways of thinking about transitivity…





Treatment A must be similar when it appears in AB and AC trials

For example, is it plausible

- when A is placebo given in different forms (e.g. injection versus pill)?
- when A is a drug given in different doses?

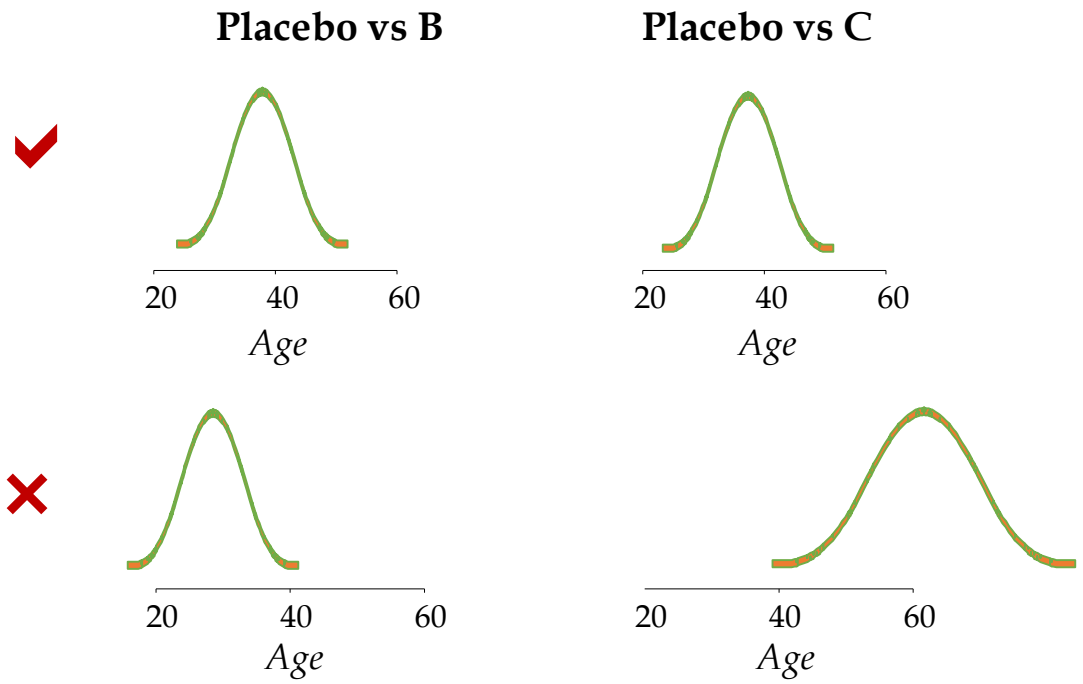
Ways of thinking about transitivity…

- Consider whether 'missing' arms are likely missing at random
  - AC trials do not have B arms and AB trials do not have treatment C
  - Is this reasonable? In some clinical areas patients would never receive alternative treatments
    - e.g. Sequencing of drugs

- Consider if all treatments are "jointly randomizable"
  - The treatments need to be genuinely competing alternatives
  - It should possible to imagine a randomized trial comparing all treatments in the network
  - Could patients have been randomly allocated to any of the treatments?
    - e.g. first- and second-line chemotherapy regimens

Ways of thinking about transitivity…

- Consider the distribution of possible effect modifiers of the relative treatment effects in AC and AB trials
  - identify a priori potential effect modifiers and compare how they are distributed across comparisons (see data extraction)
    - e.g. patients, trial protocols, doses, administration, etc. should be similar in ways which might modify the treatment effect



Thinking about transitivity

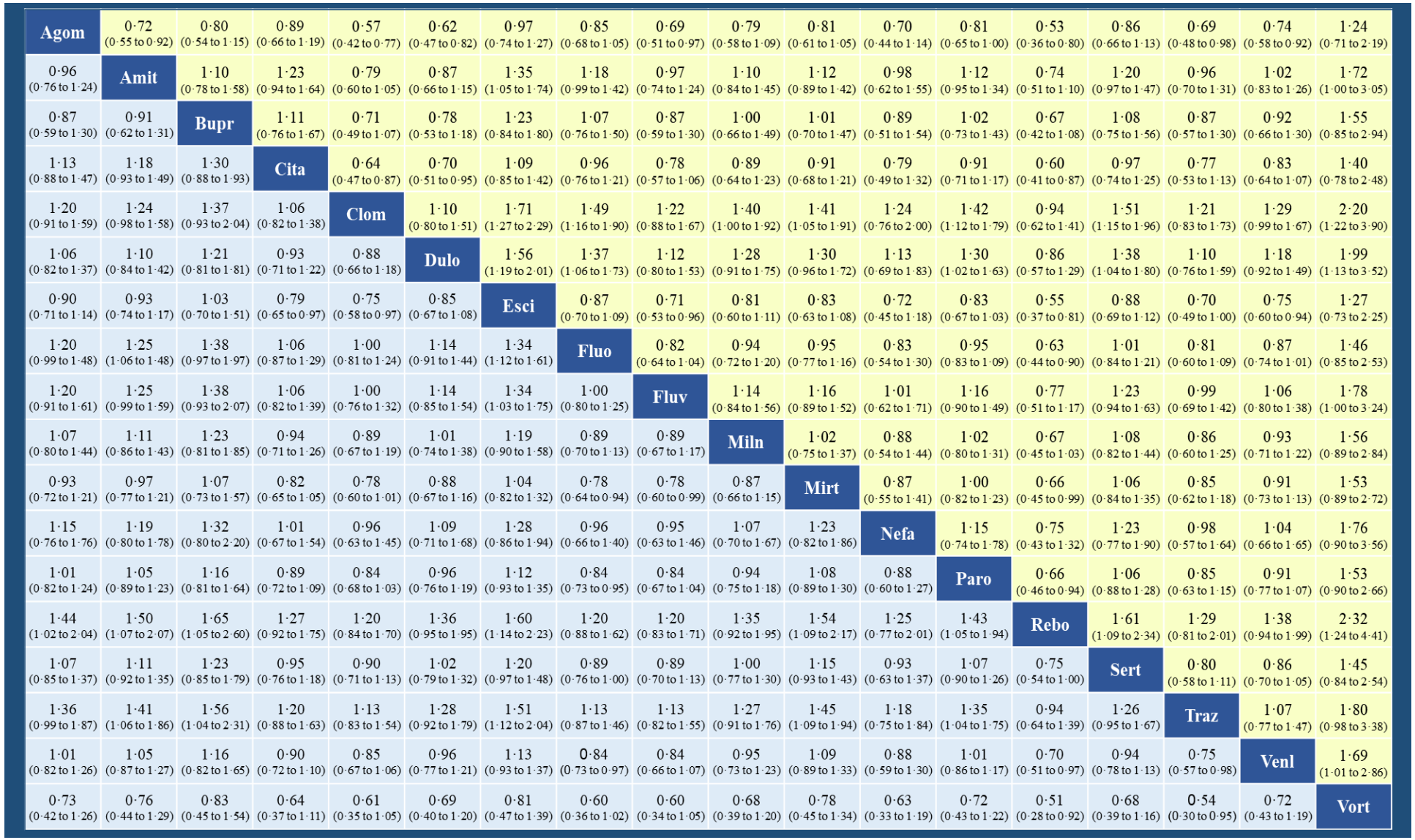
In the outset	When you find the studies	When you extract the outcomes
The treatments we compare are *in principle* jointly randomizable	The groups of studies that compare them do not differ with respect to the distribution of effect modifiers	Direct and indirect treatment effects are in statistical agreement
They have the same indication I can imagine a mega-trial with all treatments being compared etc.	You can test this if you have enough studies per comparison	Various statistical tests

Cipriani et al. ***Ann Int Med*** *2013*

Results from network meta-analysis

Example: Antidepressants for major depression

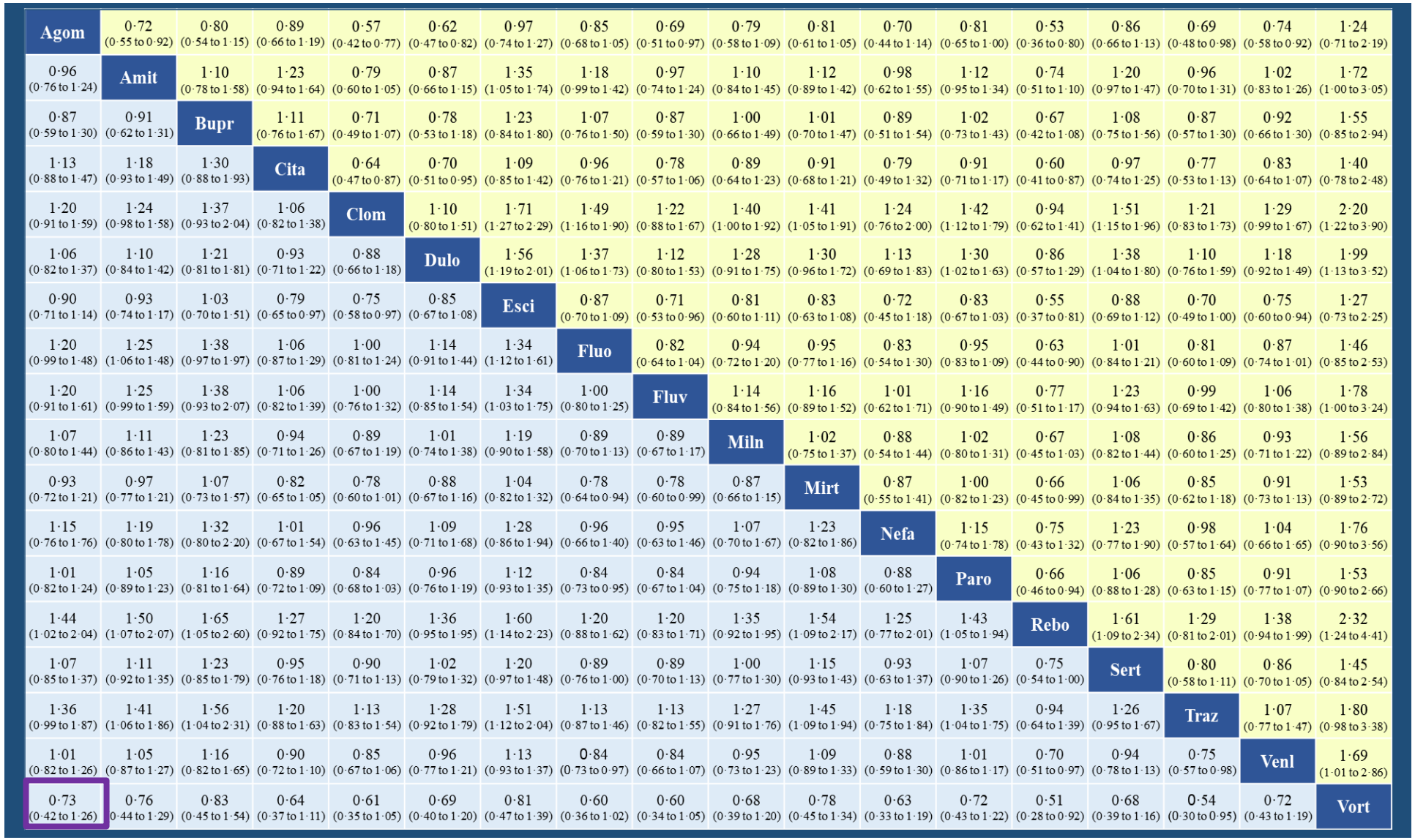
Efficacy



Agom	0·72 (0·55 to 0·92)	0·80 (0·54 to 1·15)	0·89 (0·66 to 1·19)	0·57 (0·42 to 0·77)	0·62 (0·47 to 0·82)	0·97 (0·74 to 1·27)	0·85 (0·68 to 1·05)	0·69 (0·51 to 0·97)	0·79 (0·58 to 1·09)	0·81 (0·61 to 1·05)	0·70 (0·44 to 1·14)	0·81 (0·65 to 1·00)	0·53 (0·36 to 0·80)	0·86 (0·66 to 1·13)	0·69 (0·48 to 0·98)	0·74 (0·58 to 0·92)	1·24 (0·71 to 2·19)
0·96 (0·76 to 1·24)	Amit	1·10 (0·78 to 1·58)	1·23 (0·94 to 1·64)	0·79 (0·60 to 1·05)	0·87 (0·66 to 1·15)	1·35 (1·05 to 1·74)	1·18 (0·99 to 1·42)	0·97 (0·74 to 1·24)	1·10 (0·84 to 1·45)	1·12 (0·89 to 1·42)	0·98 (0·62 to 1·55)	1·12 (0·95 to 1·34)	0·74 (0·51 to 1·10)	1·20 (0·97 to 1·47)	0·96 (0·70 to 1·31)	1·02 (0·83 to 1·26)	1·72 (1·00 to 3·05)
0·87 (0·59 to 1·30)	0·91 (0·62 to 1·31)	Bupr	1·11 (0·76 to 1·67)	0·71 (0·49 to 1·07)	0·78 (0·53 to 1·18)	1·23 (0·84 to 1·80)	1·07 (0·76 to 1·50)	0·87 (0·59 to 1·30)	1·00 (0·66 to 1·49)	1·01 (0·70 to 1·47)	0·89 (0·51 to 1·54)	1·02 (0·73 to 1·43)	0·67 (0·42 to 1·08)	1·08 (0·75 to 1·56)	0·87 (0·57 to 1·30)	0·92 (0·66 to 1·30)	1·55 (0·85 to 2·94)
1·13 (0·88 to 1·47)	1·18 (0·93 to 1·49)	1·30 (0·88 to 1·93)	Cita	0·64 (0·47 to 0·87)	0·70 (0·51 to 0·95)	1·09 (0·85 to 1·42)	0·96 (0·76 to 1·21)	0·78 (0·57 to 1·06)	0·89 (0·64 to 1·23)	0·91 (0·68 to 1·21)	0·79 (0·49 to 1·32)	0·91 (0·71 to 1·17)	0·60 (0·41 to 0·87)	0·97 (0·74 to 1·25)	0·77 (0·53 to 1·13)	0·83 (0·64 to 1·07)	1·40 (0·78 to 2·48)
1·20 (0·91 to 1·59)	1·24 (0·98 to 1·58)	1·37 (0·93 to 2·04)	1·06 (0·82 to 1·38)	Clom	1·10 (0·80 to 1·51)	1·71 (1·27 to 2·29)	1·49 (1·16 to 1·90)	1·22 (0·88 to 1·67)	1·40 (1·00 to 1·92)	1·41 (1·05 to 1·91)	1·24 (0·76 to 2·00)	1·42 (1·12 to 1·79)	0·94 (0·62 to 1·41)	1·51 (1·15 to 1·96)	1·21 (0·83 to 1·73)	1·29 (0·99 to 1·67)	2·20 (1·22 to 3·90)
1·06 (0·82 to 1·37)	1·10 (0·84 to 1·42)	1·21 (0·81 to 1·81)	0·93 (0·71 to 1·22)	0·88 (0·66 to 1·18)	Dulo	1·56 (1·19 to 2·01)	1·37 (1·06 to 1·73)	1·12 (0·80 to 1·53)	1·28 (0·91 to 1·75)	1·30 (0·96 to 1·72)	1·13 (0·69 to 1·83)	1·30 (1·02 to 1·63)	0·86 (0·57 to 1·29)	1·38 (1·04 to 1·80)	1·10 (0·76 to 1·59)	1·18 (0·92 to 1·49)	1·99 (1·13 to 3·52)
0·90 (0·71 to 1·14)	0·93 (0·74 to 1·17)	1·03 (0·70 to 1·51)	0·79 (0·65 to 0·97)	0·75 (0·58 to 0·97)	0·85 (0·67 to 1·08)	Esci	0·87 (0·70 to 1·09)	0·71 (0·53 to 0·96)	0·81 (0·60 to 1·11)	0·83 (0·63 to 1·08)	0·72 (0·45 to 1·18)	0·83 (0·67 to 1·03)	0·55 (0·37 to 0·81)	0·88 (0·69 to 1·12)	0·70 (0·49 to 1·00)	0·75 (0·60 to 0·94)	1·27 (0·73 to 2·25)
1·20 (0·99 to 1·48)	1·25 (1·06 to 1·48)	1·38 (0·97 to 1·97)	1·06 (0·87 to 1·29)	1·00 (0·81 to 1·24)	1·14 (0·91 to 1·44)	1·34 (1·12 to 1·61)	Fluo	0·82 (0·64 to 1·04)	0·94 (0·72 to 1·20)	0·95 (0·77 to 1·16)	0·83 (0·54 to 1·30)	0·95 (0·83 to 1·09)	0·63 (0·44 to 0·90)	1·01 (0·84 to 1·21)	0·81 (0·60 to 1·09)	0·87 (0·74 to 1·01)	1·46 (0·85 to 2·53)
1·20 (0·91 to 1·61)	1·25 (0·99 to 1·59)	1·38 (0·93 to 2·07)	1·06 (0·82 to 1·39)	1·00 (0·76 to 1·32)	1·14 (0·85 to 1·54)	1·34 (1·03 to 1·75)	1·00 (0·80 to 1·25)	Fluv	1·14 (0·84 to 1·56)	1·16 (0·89 to 1·52)	1·01 (0·62 to 1·71)	1·16 (0·90 to 1·49)	0·77 (0·51 to 1·17)	1·23 (0·94 to 1·63)	0·99 (0·69 to 1·42)	1·06 (0·80 to 1·38)	1·78 (1·00 to 3·24)
1·07 (0·80 to 1·44)	1·11 (0·86 to 1·43)	1·23 (0·81 to 1·85)	0·94 (0·71 to 1·26)	0·89 (0·67 to 1·19)	1·01 (0·74 to 1·38)	1·19 (0·90 to 1·58)	0·89 (0·70 to 1·13)	0·89 (0·67 to 1·17)	Miln	1·02 (0·75 to 1·37)	0·88 (0·54 to 1·44)	1·02 (0·80 to 1·31)	0·67 (0·45 to 1·03)	1·08 (0·82 to 1·44)	0·86 (0·60 to 1·25)	0·93 (0·71 to 1·22)	1·56 (0·89 to 2·84)
0·93 (0·72 to 1·21)	0·97 (0·77 to 1·21)	1·07 (0·73 to 1·57)	0·82 (0·65 to 1·05)	0·78 (0·60 to 1·01)	0·88 (0·67 to 1·16)	1·04 (0·82 to 1·32)	0·78 (0·64 to 0·94)	0·78 (0·60 to 0·99)	0·87 (0·66 to 1·15)	Mirt	0·87 (0·55 to 1·41)	1·00 (0·82 to 1·23)	0·66 (0·45 to 0·99)	1·06 (0·84 to 1·35)	0·85 (0·62 to 1·18)	0·91 (0·73 to 1·13)	1·53 (0·89 to 2·72)
1·15 (0·76 to 1·76)	1·19 (0·80 to 1·78)	1·32 (0·80 to 2·20)	1·01 (0·67 to 1·54)	0·96 (0·63 to 1·45)	1·09 (0·71 to 1·68)	1·28 (0·86 to 1·94)	0·96 (0·66 to 1·40)	0·95 (0·63 to 1·46)	1·07 (0·70 to 1·67)	1·23 (0·82 to 1·86)	Nefa	1·15 (0·74 to 1·78)	0·75 (0·43 to 1·32)	1·23 (0·77 to 1·90)	0·98 (0·57 to 1·64)	1·04 (0·66 to 1·65)	1·76 (0·90 to 3·56)
1·01 (0·82 to 1·24)	1·05 (0·89 to 1·23)	1·16 (0·81 to 1·64)	0·89 (0·72 to 1·09)	0·84 (0·68 to 1·03)	0·96 (0·76 to 1·19)	1·12 (0·93 to 1·35)	0·84 (0·73 to 0·95)	0·84 (0·67 to 1·04)	0·94 (0·75 to 1·18)	1·08 (0·89 to 1·30)	0·88 (0·60 to 1·27)	Paro	0·66 (0·46 to 0·94)	1·06 (0·88 to 1·28)	0·85 (0·63 to 1·15)	0·91 (0·77 to 1·07)	1·53 (0·90 to 2·66)
1·44 (1·02 to 2·04)	1·50 (1·07 to 2·07)	1·65 (1·05 to 2·60)	1·27 (0·92 to 1·75)	1·20 (0·84 to 1·70)	1·36 (0·95 to 1·95)	1·60 (1·14 to 2·23)	1·20 (0·88 to 1·62)	1·20 (0·83 to 1·71)	1·35 (0·92 to 1·95)	1·54 (1·09 to 2·17)	1·25 (0·77 to 2·01)	1·43 (1·05 to 1·94)	Rebo	1·61 (1·09 to 2·34)	1·29 (0·81 to 2·01)	1·38 (0·94 to 1·99)	2·32 (1·24 to 4·41)
1·07 (0·85 to 1·37)	1·11 (0·92 to 1·35)	1·23 (0·85 to 1·79)	0·95 (0·76 to 1·18)	0·90 (0·71 to 1·13)	1·02 (0·79 to 1·32)	1·20 (0·97 to 1·48)	0·89 (0·76 to 1·00)	0·89 (0·70 to 1·13)	1·00 (0·77 to 1·30)	1·15 (0·93 to 1·43)	0·93 (0·63 to 1·37)	1·07 (0·90 to 1·26)	0·75 (0·54 to 1·00)	Sert	0·80 (0·58 to 1·11)	0·86 (0·70 to 1·05)	1·45 (0·84 to 2·54)
1·36 (0·99 to 1·87)	1·41 (1·06 to 1·86)	1·56 (1·04 to 2·31)	1·20 (0·88 to 1·63)	1·13 (0·83 to 1·54)	1·28 (0·92 to 1·79)	1·51 (1·12 to 2·04)	1·13 (0·87 to 1·46)	1·13 (0·82 to 1·55)	1·27 (0·91 to 1·76)	1·45 (1·09 to 1·94)	1·18 (0·75 to 1·84)	1·35 (1·04 to 1·75)	0·94 (0·64 to 1·39)	1·26 (0·95 to 1·67)	Traz	1·07 (0·77 to 1·47)	1·80 (0·98 to 3·38)
1·01 (0·82 to 1·26)	1·05 (0·87 to 1·27)	1·16 (0·82 to 1·65)	0·90 (0·72 to 1·10)	0·85 (0·67 to 1·06)	0·96 (0·77 to 1·21)	1·13 (0·93 to 1·37)	0·84 (0·73 to 0·97)	0·84 (0·66 to 1·07)	0·95 (0·73 to 1·23)	1·09 (0·89 to 1·33)	0·88 (0·59 to 1·30)	1·01 (0·86 to 1·17)	0·70 (0·51 to 0·97)	0·94 (0·78 to 1·13)	0·75 (0·57 to 0·98)	Venl	1·69 (1·01 to 2·86)
0·73 (0·42 to 1·26)	0·76 (0·44 to 1·29)	0·83 (0·45 to 1·54)	0·64 (0·37 to 1·11)	0·61 (0·35 to 1·05)	0·69 (0·40 to 1·20)	0·81 (0·47 to 1·39)	0·60 (0·36 to 1·02)	0·60 (0·34 to 1·05)	0·68 (0·39 to 1·20)	0·78 (0·45 to 1·34)	0·63 (0·33 to 1·19)	0·72 (0·43 to 1·22)	0·51 (0·28 to 0·92)	0·68 (0·39 to 1·16)	0·54 (0·30 to 0·95)	0·72 (0·43 to 1·19)	Vort

Acceptability

Translating relative effects into probabilities



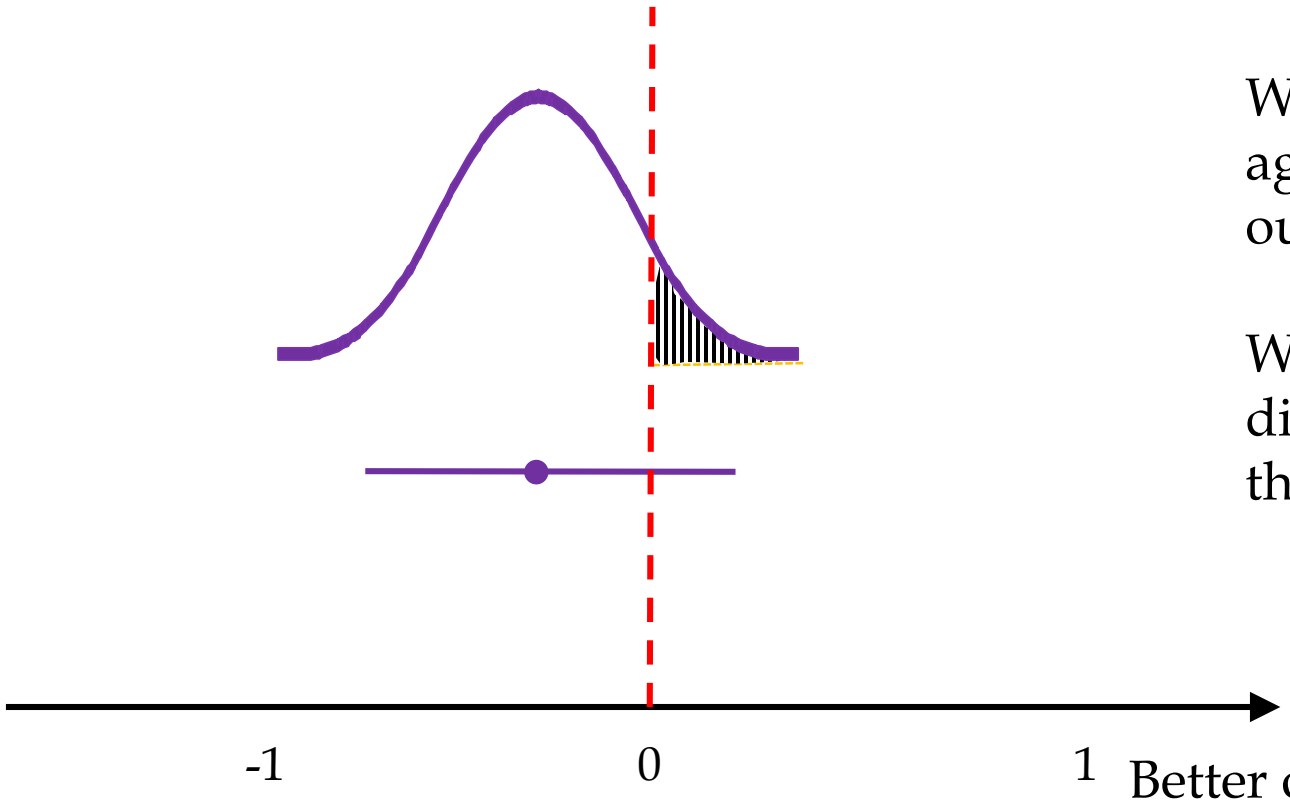
Agom	0·72 (0·55 to 0·92)	0·80 (0·54 to 1·15)	0·89 (0·66 to 1·19)	0·57 (0·42 to 0·77)	0·62 (0·47 to 0·82)	0·97 (0·74 to 1·27)	0·85 (0·68 to 1·05)	0·69 (0·51 to 0·97)	0·79 (0·58 to 1·09)	0·81 (0·61 to 1·05)	0·70 (0·44 to 1·14)	0·81 (0·65 to 1·00)	0·53 (0·36 to 0·80)	0·86 (0·66 to 1·13)	0·69 (0·48 to 0·98)	0·74 (0·58 to 0·92)	1·24 (0·71 to 2·19)
0·96 (0·76 to 1·24)	Amit	1·10 (0·78 to 1·58)	1·23 (0·94 to 1·64)	0·79 (0·60 to 1·05)	0·87 (0·66 to 1·15)	1·35 (1·05 to 1·74)	1·18 (0·99 to 1·42)	0·97 (0·74 to 1·24)	1·10 (0·84 to 1·45)	1·12 (0·89 to 1·42)	0·98 (0·62 to 1·55)	1·12 (0·95 to 1·34)	0·74 (0·51 to 1·10)	1·20 (0·97 to 1·47)	0·96 (0·70 to 1·31)	1·02 (0·83 to 1·26)	1·72 (1·00 to 3·05)
0·87 (0·59 to 1·30)	0·91 (0·62 to 1·31)	Bupr	1·11 (0·76 to 1·67)	0·71 (0·49 to 1·07)	0·78 (0·53 to 1·18)	1·23 (0·84 to 1·80)	1·07 (0·76 to 1·50)	0·87 (0·59 to 1·30)	1·00 (0·66 to 1·49)	1·01 (0·70 to 1·47)	0·89 (0·51 to 1·54)	1·02 (0·73 to 1·43)	0·67 (0·42 to 1·08)	1·08 (0·75 to 1·56)	0·87 (0·57 to 1·30)	0·92 (0·66 to 1·30)	1·55 (0·85 to 2·94)
1·13 (0·88 to 1·47)	1·18 (0·93 to 1·49)	1·30 (0·88 to 1·93)	Cita	0·64 (0·47 to 0·87)	0·70 (0·51 to 0·95)	1·09 (0·85 to 1·42)	0·96 (0·76 to 1·21)	0·78 (0·57 to 1·06)	0·89 (0·64 to 1·23)	0·91 (0·68 to 1·21)	0·79 (0·49 to 1·32)	0·91 (0·71 to 1·17)	0·60 (0·41 to 0·87)	0·97 (0·74 to 1·25)	0·77 (0·53 to 1·13)	0·83 (0·64 to 1·07)	1·40 (0·78 to 2·48)
1·20 (0·91 to 1·59)	1·24 (0·98 to 1·58)	1·37 (0·93 to 2·04)	1·06 (0·82 to 1·38)	Clom	1·10 (0·80 to 1·51)	1·71 (1·27 to 2·29)	1·49 (1·16 to 1·90)	1·22 (0·88 to 1·67)	1·40 (1·00 to 1·92)	1·41 (1·05 to 1·91)	1·24 (0·76 to 2·00)	1·42 (1·12 to 1·79)	0·94 (0·62 to 1·41)	1·51 (1·15 to 1·96)	1·21 (0·83 to 1·73)	1·29 (0·99 to 1·67)	2·20 (1·22 to 3·90)
1·06 (0·82 to 1·37)	1·10 (0·84 to 1·42)	1·21 (0·81 to 1·81)	0·93 (0·71 to 1·22)	0·88 (0·66 to 1·18)	Dulo	1·56 (1·19 to 2·01)	1·37 (1·06 to 1·73)	1·12 (0·80 to 1·53)	1·28 (0·91 to 1·75)	1·30 (0·96 to 1·72)	1·13 (0·69 to 1·83)	1·30 (1·02 to 1·63)	0·86 (0·57 to 1·29)	1·38 (1·04 to 1·80)	1·10 (0·76 to 1·59)	1·18 (0·92 to 1·49)	1·99 (1·13 to 3·52)
0·90 (0·71 to 1·14)	0·93 (0·74 to 1·17)	1·03 (0·70 to 1·51)	0·79 (0·65 to 0·97)	0·75 (0·58 to 0·97)	0·85 (0·67 to 1·08)	Esci	0·87 (0·70 to 1·09)	0·71 (0·53 to 0·96)	0·81 (0·60 to 1·11)	0·83 (0·63 to 1·08)	0·72 (0·45 to 1·18)	0·83 (0·67 to 1·03)	0·55 (0·37 to 0·81)	0·88 (0·69 to 1·12)	0·70 (0·49 to 1·00)	0·75 (0·60 to 0·94)	1·27 (0·73 to 2·25)
1·20 (0·99 to 1·48)	1·25 (1·06 to 1·48)	1·38 (0·97 to 1·97)	1·06 (0·87 to 1·29)	1·00 (0·81 to 1·24)	1·14 (0·91 to 1·44)	1·34 (1·12 to 1·61)	Fluo	0·82 (0·64 to 1·04)	0·94 (0·72 to 1·20)	0·95 (0·77 to 1·16)	0·83 (0·54 to 1·30)	0·95 (0·83 to 1·09)	0·63 (0·44 to 0·90)	1·01 (0·84 to 1·21)	0·81 (0·60 to 1·09)	0·87 (0·74 to 1·01)	1·46 (0·85 to 2·53)
1·20 (0·91 to 1·61)	1·25 (0·99 to 1·59)	1·38 (0·93 to 2·07)	1·06 (0·82 to 1·39)	1·00 (0·76 to 1·32)	1·14 (0·85 to 1·54)	1·34 (1·03 to 1·75)	1·00 (0·80 to 1·25)	Fluv	1·14 (0·84 to 1·56)	1·16 (0·89 to 1·52)	1·01 (0·62 to 1·71)	1·16 (0·90 to 1·49)	0·77 (0·51 to 1·17)	1·23 (0·94 to 1·63)	0·99 (0·69 to 1·42)	1·06 (0·80 to 1·38)	1·78 (1·00 to 3·24)
1·07 (0·80 to 1·44)	1·11 (0·86 to 1·43)	1·23 (0·81 to 1·85)	0·94 (0·71 to 1·26)	0·89 (0·67 to 1·19)	1·01 (0·74 to 1·38)	1·19 (0·90 to 1·58)	0·89 (0·70 to 1·13)	0·89 (0·67 to 1·17)	Miln	1·02 (0·75 to 1·37)	0·88 (0·54 to 1·44)	1·02 (0·80 to 1·31)	0·67 (0·45 to 1·03)	1·08 (0·82 to 1·44)	0·86 (0·60 to 1·25)	0·93 (0·71 to 1·22)	1·56 (0·89 to 2·84)
0·93 (0·72 to 1·21)	0·97 (0·77 to 1·21)	1·07 (0·73 to 1·57)	0·82 (0·65 to 1·05)	0·78 (0·60 to 1·01)	0·88 (0·67 to 1·16)	1·04 (0·82 to 1·32)	0·78 (0·64 to 0·94)	0·78 (0·60 to 0·99)	0·87 (0·66 to 1·15)	Mirt	0·87 (0·55 to 1·41)	1·00 (0·82 to 1·23)	0·66 (0·45 to 0·99)	1·06 (0·84 to 1·35)	0·85 (0·62 to 1·18)	0·91 (0·73 to 1·13)	1·53 (0·89 to 2·72)
1·15 (0·76 to 1·76)	1·19 (0·80 to 1·78)	1·32 (0·80 to 2·20)	1·01 (0·67 to 1·54)	0·96 (0·63 to 1·45)	1·09 (0·71 to 1·68)	1·28 (0·86 to 1·94)	0·96 (0·66 to 1·40)	0·95 (0·63 to 1·46)	1·07 (0·70 to 1·67)	1·23 (0·82 to 1·86)	Nefa	1·15 (0·74 to 1·78)	0·75 (0·43 to 1·32)	1·23 (0·77 to 1·90)	0·98 (0·57 to 1·64)	1·04 (0·66 to 1·65)	1·76 (0·90 to 3·56)
1·01 (0·82 to 1·24)	1·05 (0·89 to 1·23)	1·16 (0·81 to 1·64)	0·89 (0·72 to 1·09)	0·84 (0·68 to 1·03)	0·96 (0·76 to 1·19)	1·12 (0·93 to 1·35)	0·84 (0·73 to 0·95)	0·84 (0·67 to 1·04)	0·94 (0·75 to 1·18)	1·08 (0·89 to 1·30)	0·88 (0·60 to 1·27)	Paro	0·66 (0·46 to 0·94)	1·06 (0·88 to 1·28)	0·85 (0·63 to 1·15)	0·91 (0·77 to 1·07)	1·53 (0·90 to 2·66)
1·44 (1·02 to 2·04)	1·50 (1·07 to 2·07)	1·65 (1·05 to 2·60)	1·27 (0·92 to 1·75)	1·20 (0·84 to 1·70)	1·36 (0·95 to 1·95)	1·60 (1·14 to 2·23)	1·20 (0·88 to 1·62)	1·20 (0·83 to 1·71)	1·35 (0·92 to 1·95)	1·54 (1·09 to 2·17)	1·25 (0·77 to 2·01)	1·43 (1·05 to 1·94)	Rebo	1·61 (1·09 to 2·34)	1·29 (0·81 to 2·01)	1·38 (0·94 to 1·99)	2·32 (1·24 to 4·41)
1·07 (0·85 to 1·37)	1·11 (0·92 to 1·35)	1·23 (0·85 to 1·79)	0·95 (0·76 to 1·18)	0·90 (0·71 to 1·13)	1·02 (0·79 to 1·32)	1·20 (0·97 to 1·48)	0·89 (0·76 to 1·00)	0·89 (0·70 to 1·13)	1·00 (0·77 to 1·30)	1·15 (0·93 to 1·43)	0·93 (0·63 to 1·37)	1·07 (0·90 to 1·26)	0·75 (0·54 to 1·00)	Sert	0·80 (0·58 to 1·11)	0·86 (0·70 to 1·05)	1·45 (0·84 to 2·54)
1·36 (0·99 to 1·87)	1·41 (1·06 to 1·86)	1·56 (1·04 to 2·31)	1·20 (0·88 to 1·63)	1·13 (0·83 to 1·54)	1·28 (0·92 to 1·79)	1·51 (1·12 to 2·04)	1·13 (0·87 to 1·46)	1·13 (0·82 to 1·55)	1·27 (0·91 to 1·76)	1·45 (1·09 to 1·94)	1·18 (0·75 to 1·84)	1·35 (1·04 to 1·75)	0·94 (0·64 to 1·39)	1·26 (0·95 to 1·67)	Traz	1·07 (0·77 to 1·47)	1·80 (0·98 to 3·38)
1·01 (0·82 to 1·26)	1·05 (0·87 to 1·27)	1·16 (0·82 to 1·65)	0·90 (0·72 to 1·10)	0·85 (0·67 to 1·06)	0·96 (0·77 to 1·21)	1·13 (0·93 to 1·37)	0·84 (0·73 to 0·97)	0·84 (0·66 to 1·07)	0·95 (0·73 to 1·23)	1·09 (0·89 to 1·33)	0·88 (0·59 to 1·30)	1·01 (0·86 to 1·17)	0·70 (0·51 to 0·97)	0·94 (0·78 to 1·13)	0·75 (0·57 to 0·98)	Venl	1·69 (1·01 to 2·86)
0·73 (0·42 to 1·26)	0·76 (0·44 to 1·29)	0·83 (0·45 to 1·54)	0·64 (0·37 to 1·11)	0·61 (0·35 to 1·05)	0·69 (0·40 to 1·20)	0·81 (0·47 to 1·39)	0·60 (0·36 to 1·02)	0·60 (0·34 to 1·05)	0·68 (0·39 to 1·20)	0·78 (0·45 to 1·34)	0·63 (0·33 to 1·19)	0·72 (0·43 to 1·22)	0·51 (0·28 to 0·92)	0·68 (0·39 to 1·16)	0·54 (0·30 to 0·95)	0·72 (0·43 to 1·19)	Vort

Efficacy

Acceptability

Comparison of treatments using probabilities

$$OR_{agom-vort} = 0.73\ (0.42,1.26)$$
$$\rightarrow \quad \ln\left(OR_{agom-vort}\right) = -0.31\ (-0.87,0.23)$$



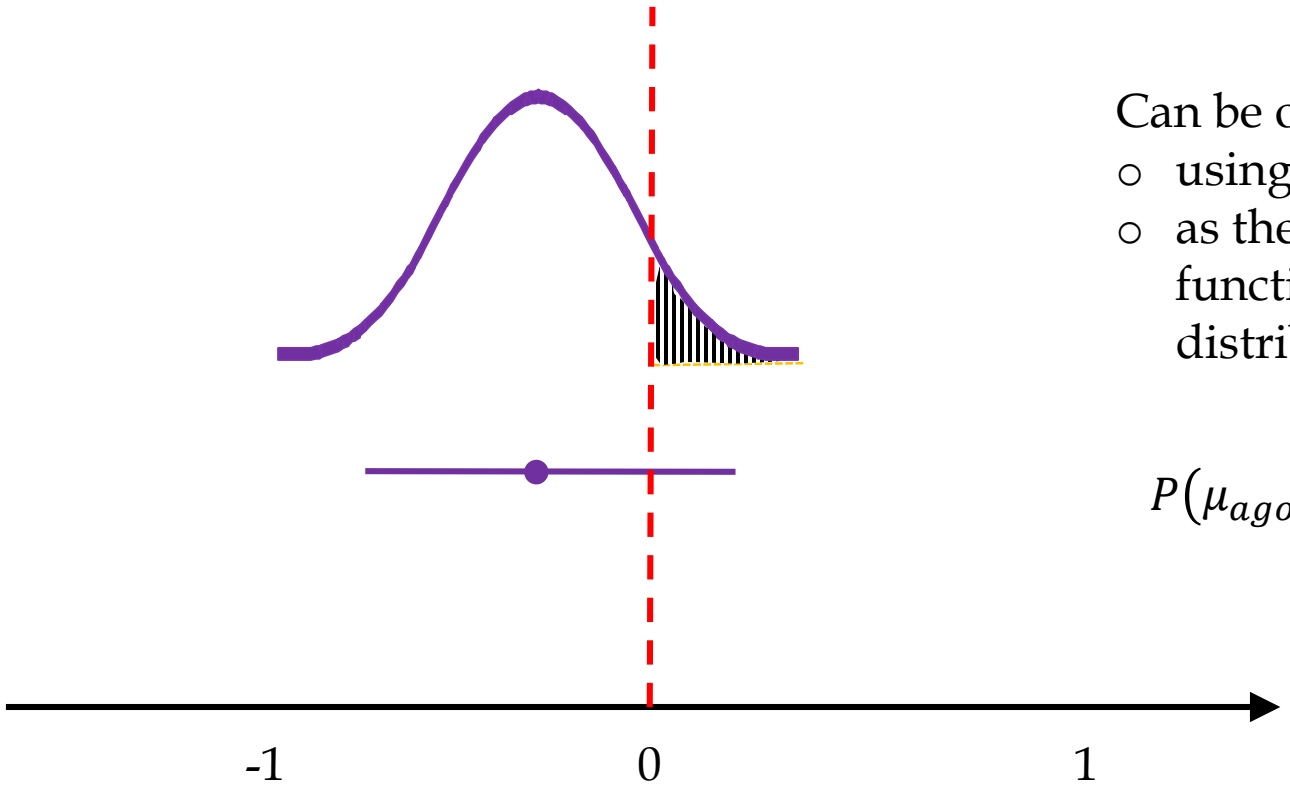
What is the probability that agomelatine produces a better outcome than vortioxetine?

OR

What is the probability that their difference in log-odds is larger than zero?

Comparison of treatments using probabilities

$$OR_{agom-vort} = 0.73\ (0.42,1.26)$$
$$\rightarrow \quad \ln\left(OR_{agom-vort}\right) = -0.31\ (-0.87,0.23)$$



Can be obtained
- using resampling methods
- as the cumulative distribution function of the standard normal distribution:

$$P\left(\mu_{agom} > \mu_{vort}\right) = \Phi\left(\frac{\hat{\mu}_{agom} - \hat{\mu}_{vort}}{sd_{agom-vort}}\right)$$

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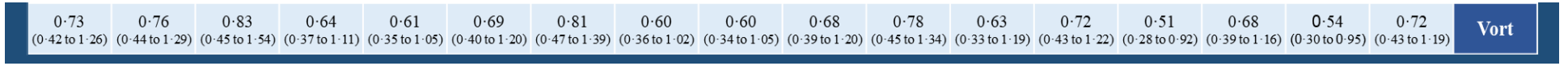
Translating relative effects into probabilities

Probabilities that vortioxetine produces a better outcome than each other treatment

88.7 86.1 73.8 95.2 96.8 91.9 79.1 97.5 96.9 92.2 83.8 92.6 90.2 99.1 93.6 98.7 91.4

Probabilities that each other treatment produces a better outcome than vortioxetine

11.3 13.9 26.2 4.8 3.2 8.1 20.9 2.5 3.1 7.8 16.2 7.4 9.8 0.9 6.4 1.3 8.6



What is P-score?

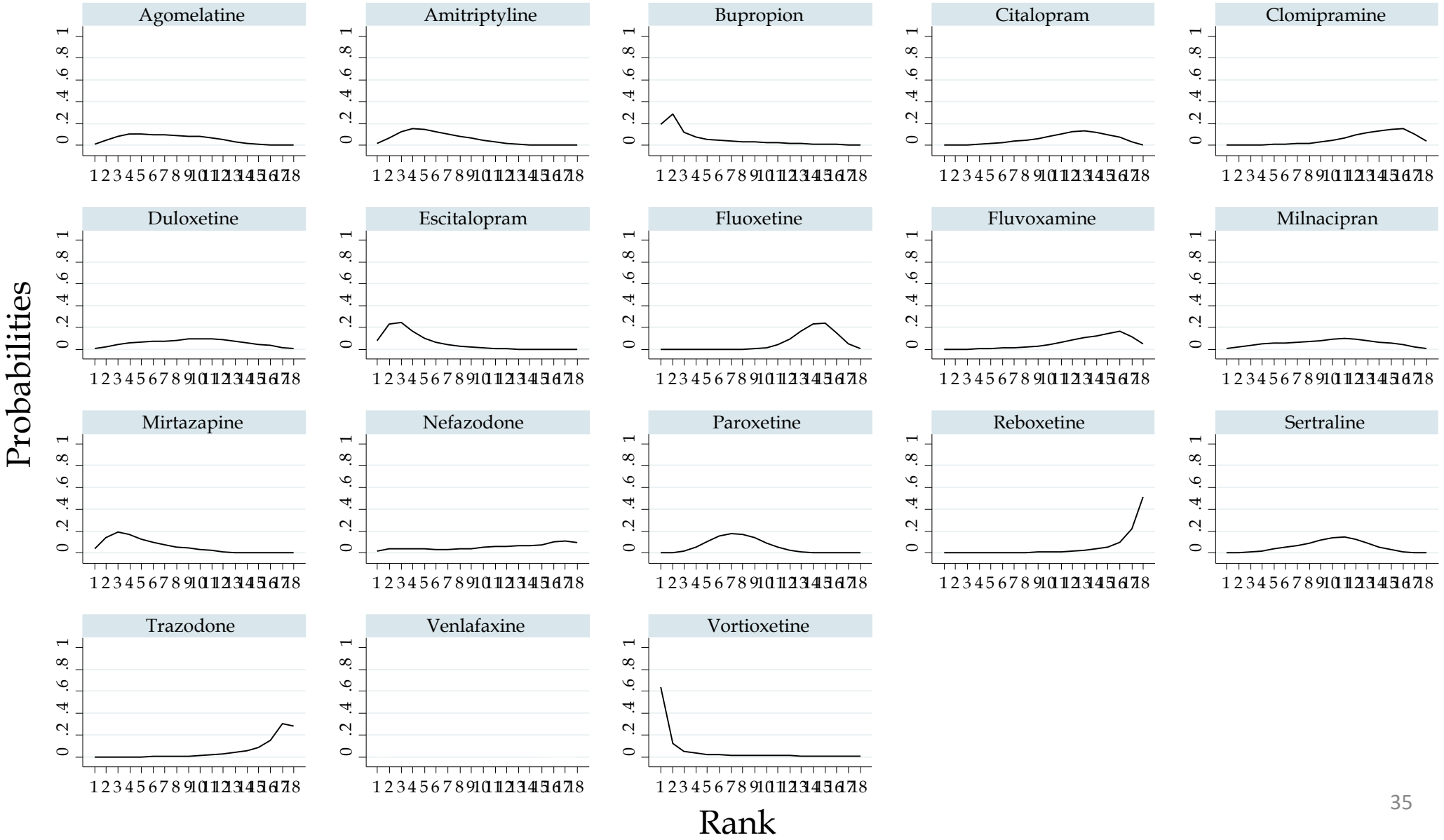
Probabilities (p) that vortioxetine produces a better outcome than each other treatment

88.7 86.1 73.8 95.2 96.8 91.9 79.1 97.5 96.9 92.2 83.8 92.6 90.2 99.1 93.6 98.7 91.4

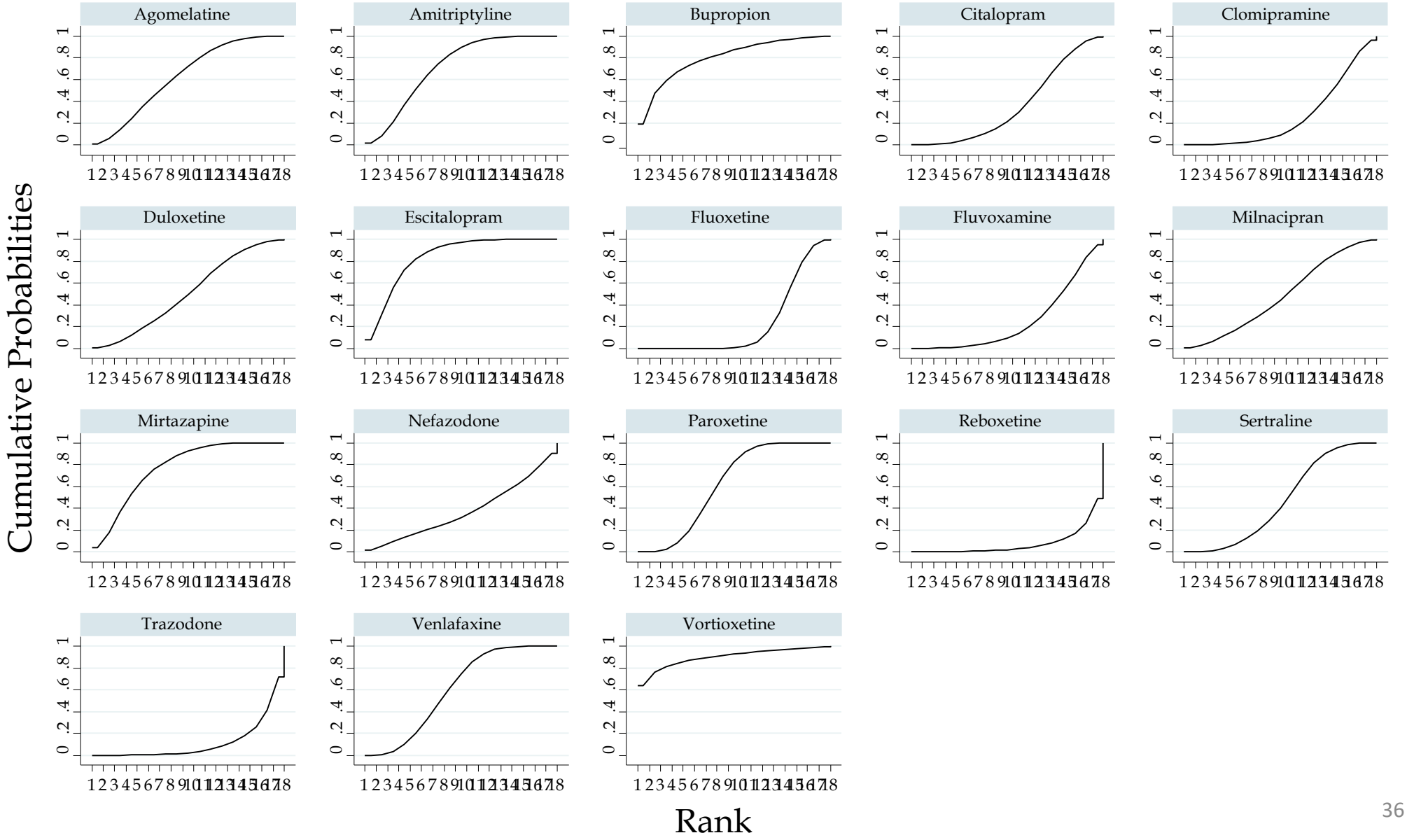
$$P - score_{vort} = \sum_{i=1, i \neq vort}^{T} \frac{p_{vort-i}}{T-1} = 91\%$$

Rücker and Schwarzer ***BMC Med Res Methodol*** *2015*

Ranking probabilities

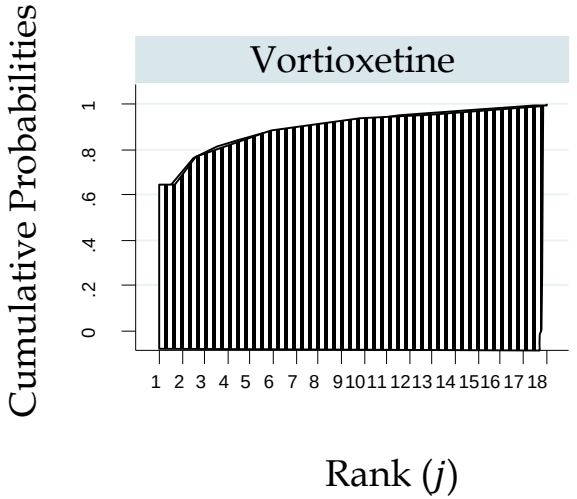


Cumulative ranking probabilities



What is SUCRA?

$$SUCRA_{vort} = \sum_{j=1}^{T-1} \frac{cump_{vort-j}}{T-1} = 91\%$$



*Salanti et al. **JCE** 2011*

What do SUCRA and P-score represent?

$$SUCRA_{vort} = \sum_{j=1}^{T-1} \frac{cump_{vort-j}}{T-1} = 91\%$$

$$P-score_{vort} = \sum_{i=1, i \neq vort}^{T} \frac{p_{vort-i}}{T-1} = 91\%$$

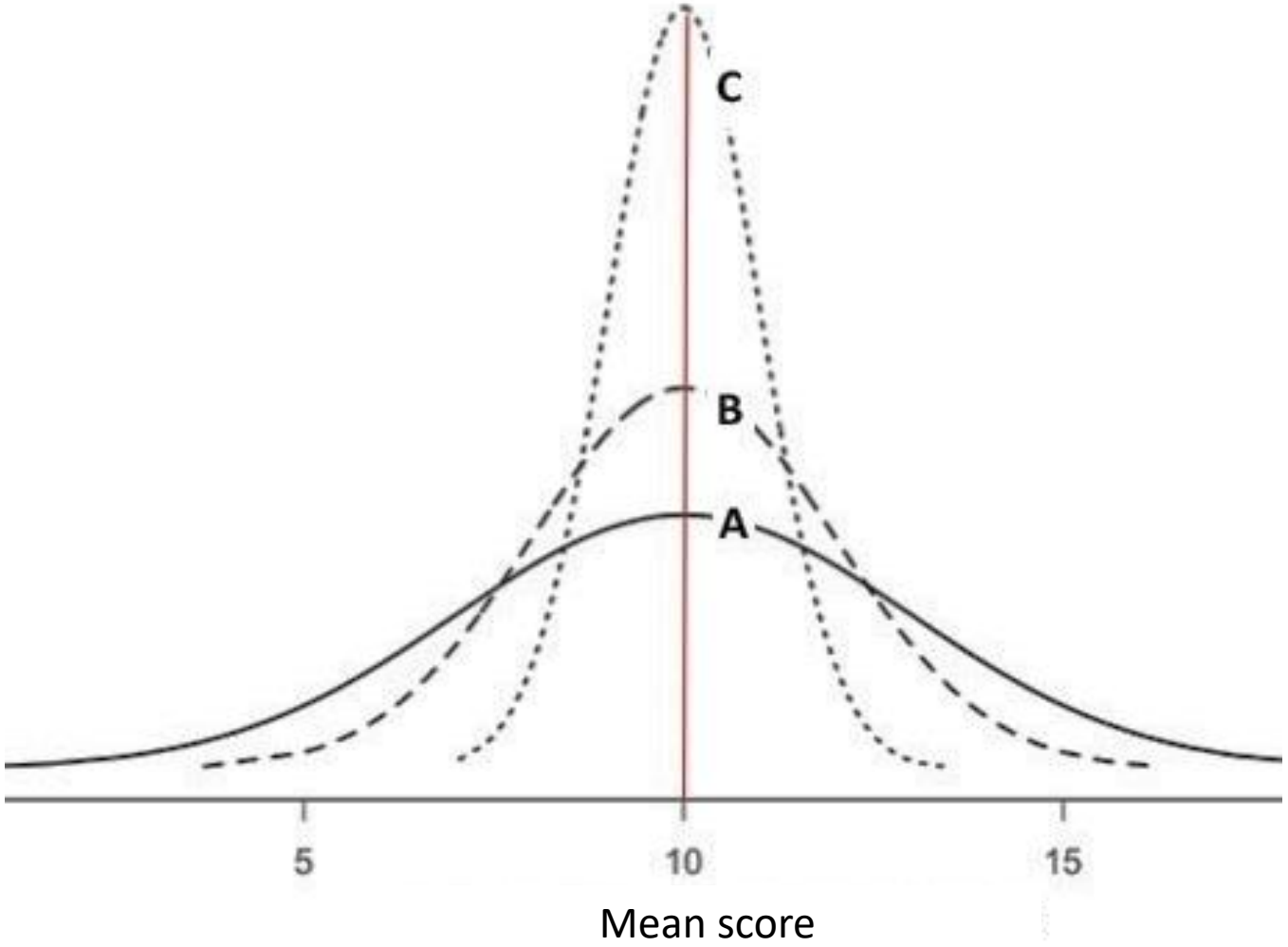
SUCRA/ P-score* of treatment *i

= The percentage of the effectiveness/safety of a treatment that would be ranked first without any uncertainty

= The percentage of treatments worse than *i*

=The mean extent of certainty that a treatment is better than the other competing treatments

Why P(best) is misleading?



Treatment	Prob of best outcome
A	40%
B	33%
C	27%

Treatments with large uncertainty can be favoured by P(best)!!

Cautious note about ranking

- Ranking measures are not substitutes for relative effect estimates

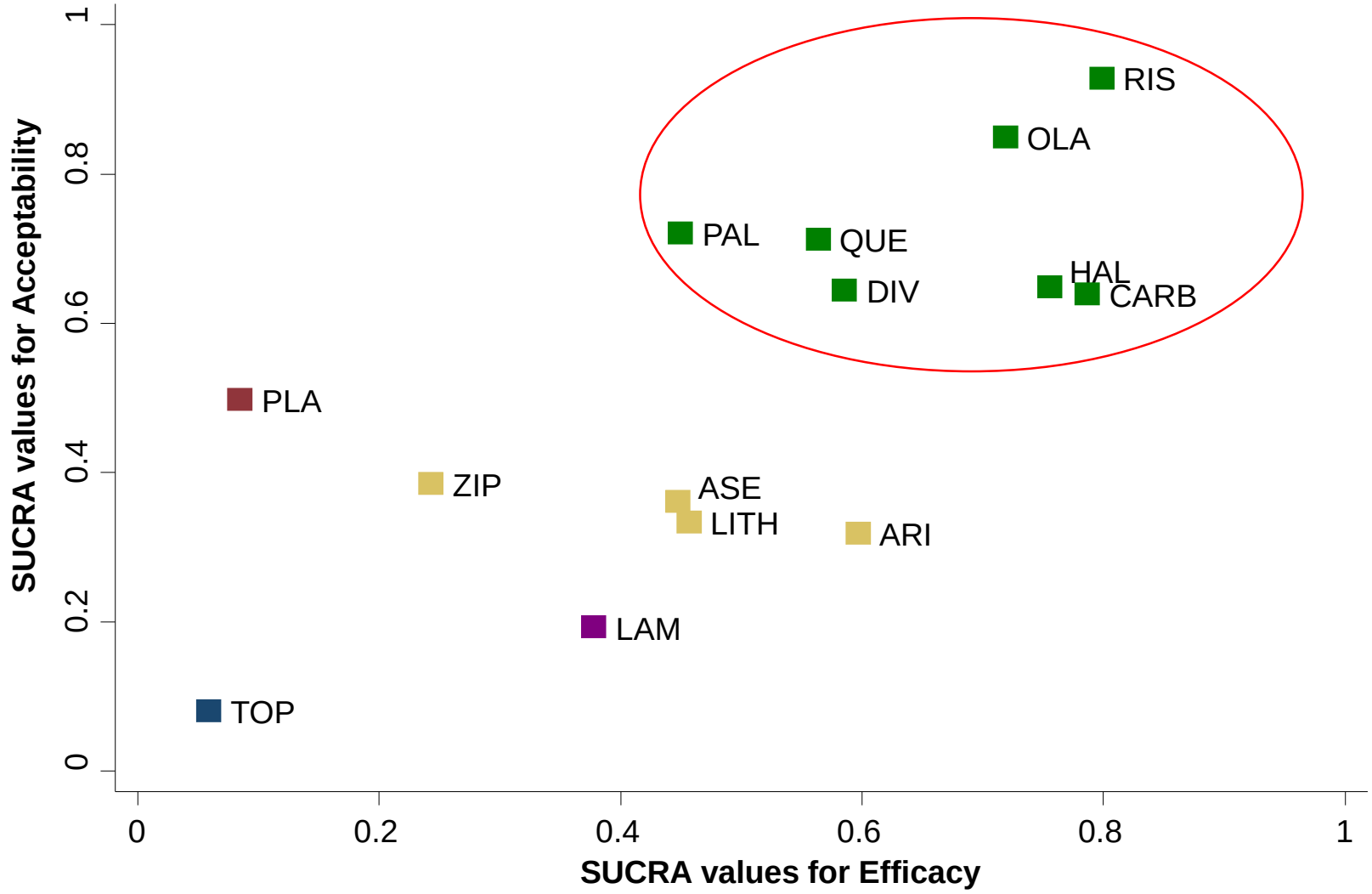
- Ranking based on SUCRAs or mean ranks accounts better for the uncertainty in relative ranking
  - Using P(best) to rank treatments can be misleading

- Ranking measures are conditional on the set of treatments being compared
  - SUCRAs and P-scores will change when only a subset of interventions are compared

- Avoid ranking when there is a lot of uncertainty in the effect estimates or when there are important differences in the uncertainty across comparisons

- Methods that allow more information in ranking are available
  - *Chaimani et al. PlosOne 2013*

Two-dimensional display for ranking



Chaimani et al. ***Plos One*** *2013*

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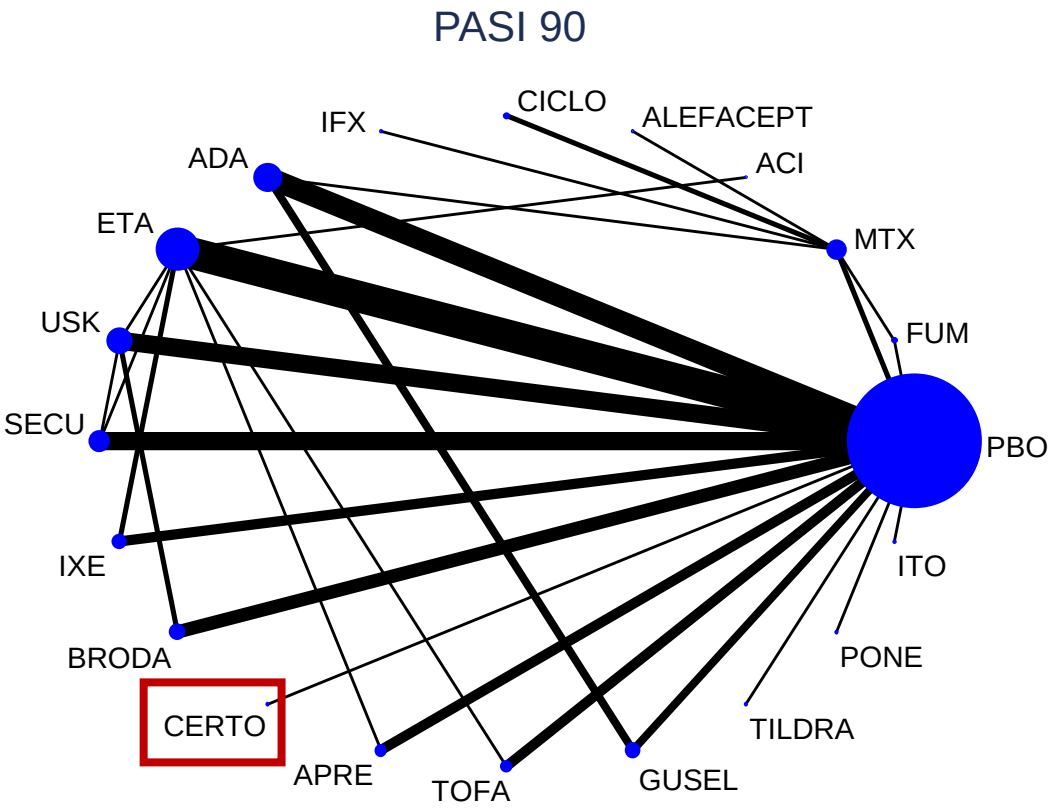
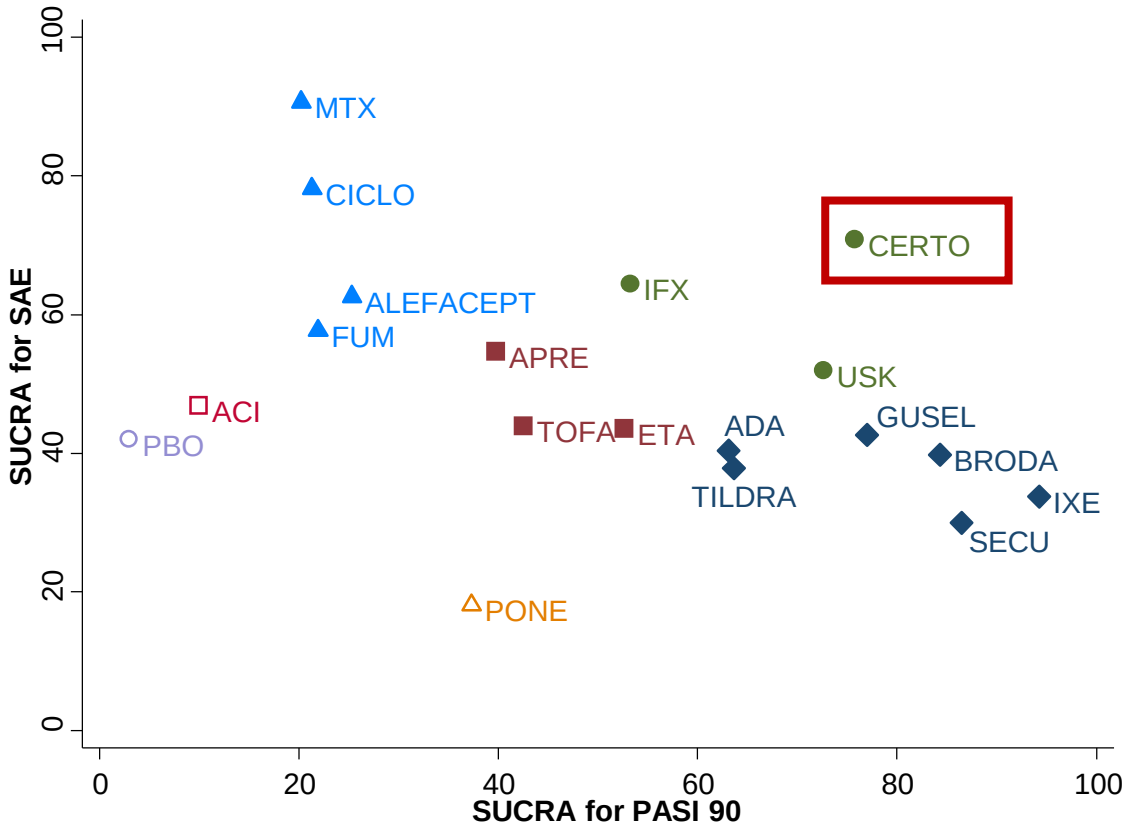
  - *Chaimani et al. PlosOne 2013*
  - *Salanti et al. PlonOne 2014*
  - *Choi et al 2019*
  - *Mavridis et al. Biometrical J 2019*
  - *Chaimani et al. MedRxiv 2019 [under revision]*

Motivating example

Systemic pharmacological treatments for chronic plaque psoriasis





Treatment ranking as a discrete stochastic process

- Markov process S with a countable state space
- every treatment (node) $i = 1, \dots, N$ is a state s_i
- S starts at $t = 1$ when we start 'moving' between the N treatment options
- movement from i to j implies that treatment i was not 'satisfying' and we select j as a potentially more beneficial treatment
- $l_i^{(t)}$ the probability of selecting treatment i at time (step) t
- $\mathbf{Q^{(0)}} = \left(l_1^{(0)}, \dots, l_N^{(0)}\right)'$ the initial state probability vector

Transition probabilities

- $p_{i\to j}^{(t)}$ the probability of selecting treatment j at $t+1$ after having selected treatment i at t

- given that $\sum_{j=1}^{N} p_{i\to j}^{(t)} = 1$, we define

$$p_{i\to j}^{(1)} = \frac{p_{j>i}}{\sum_{i=1}^{N} p_{j>i}}, \qquad p_{i\to i}^{(1)} = 0$$

  where $p_{j>i}$ is the probability that j is 'better' than i with $p_{i>j} = \Phi\left(\frac{\hat{\mu}_i - \hat{\mu}_j}{\sigma_{ij}}\right)$

- S has a unique stationary distribution $\boldsymbol{\pi} = \left(l_1^{(t\to\infty)}, \dots, l_N^{(t\to\infty)}\right)'$ with $\boldsymbol{\pi} = \mathbf{A}\boldsymbol{\pi}$ $\left(\mathbf{A} \equiv \mathbf{A}^{(1)}, \mathbf{A}^{(t)} = \mathbf{A}^{t}\right)$

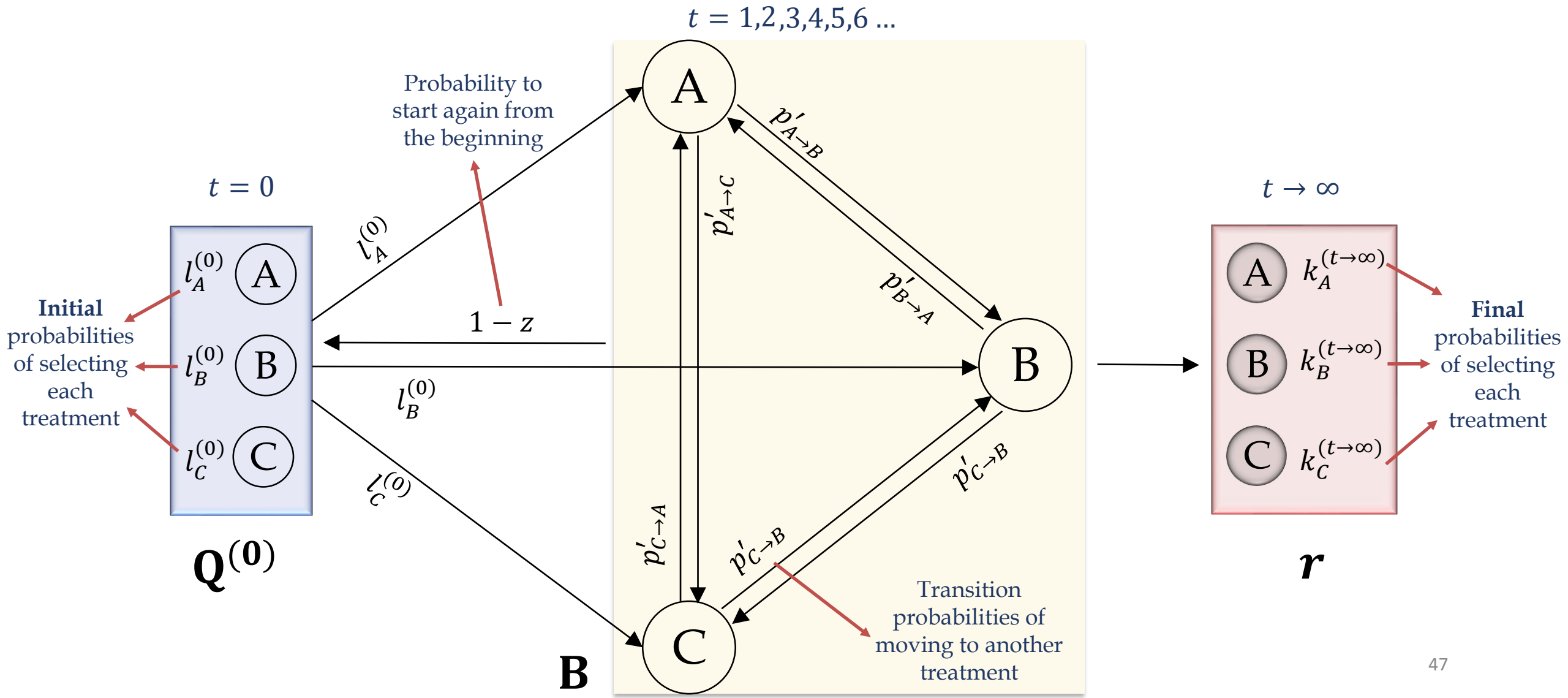
Incorporating the initial probability distribution

- special case of a Markov Chain: at any t there is a probability of starting again the process S from $\mathbf{Q^{(0)}}$
- $z \in (0,1)$ the probability that S continues at t according to $\mathbf{A^t}$ and $(z-1)$ the probability that starts again from $\mathbf{Q^{(0)}}$
- modified transition probabilities $p'_{i\to j} = zp_{i\to j} + (1-z)l_j^{(0)}$, $p'_{i\to i} = (1-z)l_i^{(0)}$
- modified transition matrix $\mathbf{B} = \left(\mathrm{z}\mathbf{A}' + (1-\mathrm{z})\mathbf{Q^{(0)}}\mathbf{1}'\right)'$
- S has again a unique stationary distribution $\boldsymbol{r} = \left(k_1^{(t\to\infty)}, \dots, k_N^{(t\to\infty)}\right)'$ with

$$\boldsymbol{r} = \mathbf{B}\boldsymbol{r}$$

Probability of selecting a treatment to recommend (POST-R)

Graphical representation of the POST-R approach



Defining the $Q^{(0)}$ vector

- Confidence/certainty/quality of the evidence
  - evidence on some of the treatments might be less 'trustworthy' than for others

Application to the psoriasis network

ACI																		
3.3	ADA																	
17.1	98.4	ALEFACEPT																
8.3	97.3	19.9	APRE															
1.3	1.1	0.2	0.0	BRODA														
3.5	31.1	6.9	13.2	51.4	CERTO													
17.8	100	56.6	90.4	100.0	95.4	CICLO												
5.0	93.1	6.8	11.9	100.0	79.3	0.9	ETA											
17.3	99.9	54	89.8	100.0	95.2	48.1	99.0	FUM										
1.9	0.0	0.3	0.2	77.7	56.1	0.0	0.2	0.0	GUSEL									
5.3	81.9	4.0	20.4	98.3	77.2	0.1	46.2	2.3	97.7	IFX								
10.8	55.4	25.2	37.3	69.5	65.5	22.3	46.4	22.8	64.7	47.5	ITO							
0.8	0.1	0.1	0.0	5.2	39.2	0.0	0.0	0.0	4.4	0.3	24.8	IXE						
17.7	100	59.0	94.4	100.0	96.1	52.9	99.9	53.7	100.0	100.0	78.4	100.0	MTX					
49.5	100	99.4	100	100.0	99.9	100	100	100.0	100.0	100.0	96.1	100.0	100.0	PBO				
12.1	86.6	32.9	57.7	96.8	85.8	26.9	75.2	27.9	94.2	74.7	65.2	98.5	25.0	0.4	PONE			
1.2	0.5	0.1	0.0	36.5	46.9	0.0	0.0	0.0	16.0	1.0	29.4	91.7	0.0	0.0	2.7	SECU		
5.9	48.0	13.6	24.6	68.6	62.6	10.2	35.6	10.5	61.5	37.5	44.4	76.5	9.2	0.3	24.1	70.1	TILDRA	
7.0	98.9	13.8	37.2	100.0	85.3	4.0	94.5	4.2	100.0	76.7	60.1	100.0	1.0	0.0	36.4	100	72.7	TOFA
2.0	9.7	0.7	0.1	99.9	58.3	0.0	0.0	0.0	59.1	6.4	36.7	100.0	0.0	0.0	6.4	99.9	40.5	0.0	USK

PASI 90

Application to the psoriasis network

ACI																		
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17.1	98.4	ALEFACEPT																
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2.0	9.7	0.7	0.1	99.9	58.3	0.0	0.0	0.0	59.1	6.4	36.7	100.0	0.0	0.0	6.4	99.9	40.5	0.0	USK

	Confidence
	High
	Moderate
	Low
	Very low

PASI 90

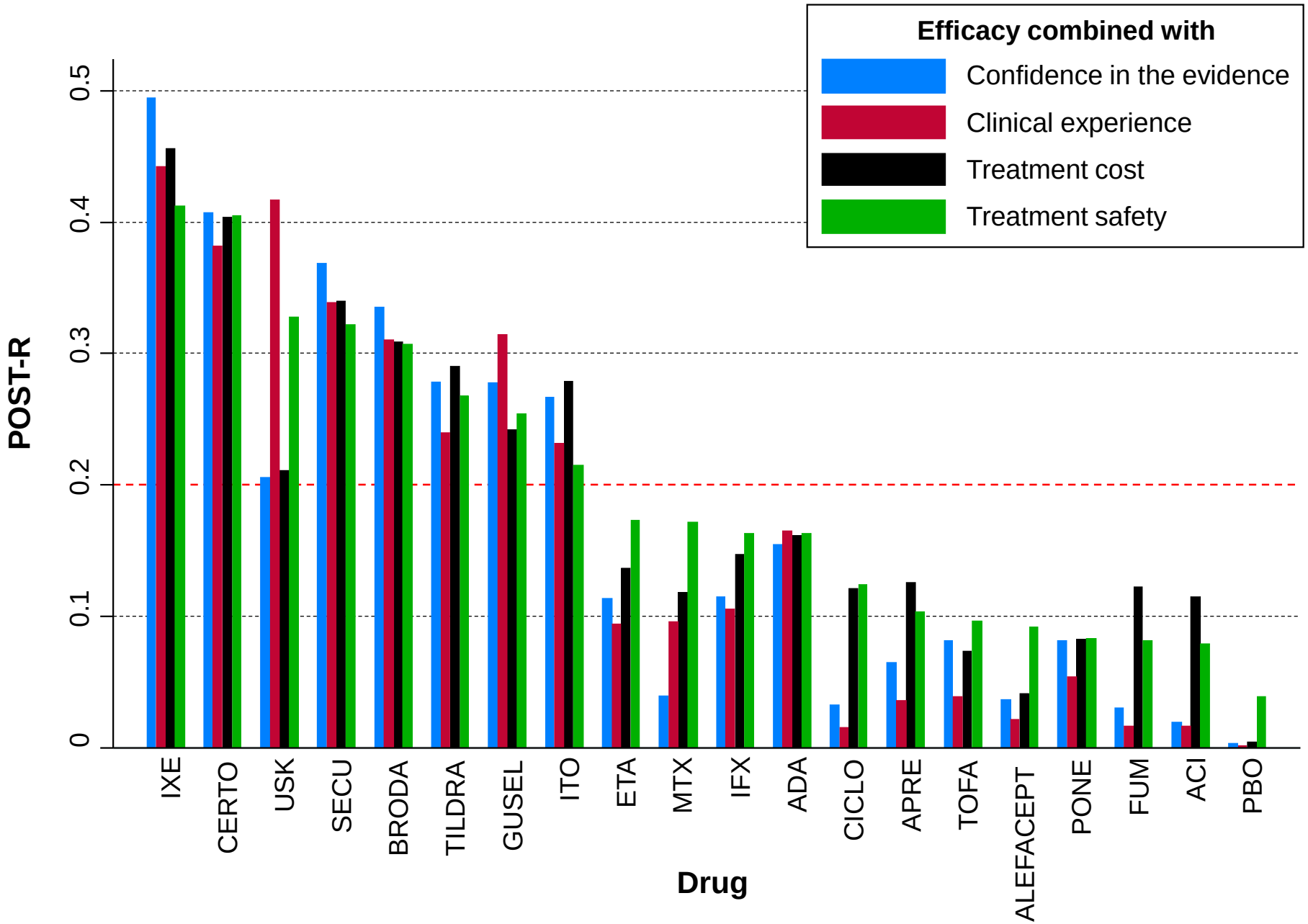
Defining the $Q^{(0)}$ vector

- Confidence/certainty/quality of the evidence
  - evidence on some of the treatments might be less 'trustworthy' than for others
- Clinical experience
  - prior information from clinical practice is important and is not always in agreement with study results as the latter may lack power, have a short follow-up period
- Safety of treatments
  - efficacy and safety should always be considered jointly when forming recommendations
- Cost of the treatments
  - cheaper treatments might be preferable if they yield similar outcomes to slightly more effective, but expensive, ones

Defining the probability *z*

- Not straightforward how to select the *z* value
  - depends also on the clinical setting and the available data
- Sensitivity analysis on range of values
- Informed by expert opinion
- Can follow a distribution

Results


Efficacy combined with
Confidence in the evidence
Clinical experience
Treatment cost
Treatment safety
POST-R
0
0.1
0.2
0.3
0.4
0.5
IXE
CERTO
USK
SECU
BRODA
TILDRA
GUSEL
ITO
ETA
MTX
IFX
ADA
CICLO
APRE
TOFA
ALEFACEPT
PONE
FUM
ACI
PBO
Drug

Limitations

- The definition of the vector $\mathbf{Q}^{(\mathbf{0})}$ and the probability z is subjective to some degree
- The expert opinion was obtained after the publication of the original network meta-analysis and we used only one clinician
- There might be additional characteristics affecting treatment selection not considered in our application
- Our results our only illustrative of the method and do not aim to draw clinical inferences

Discussion

- Treatment ranking should represent the process of considering treatments for selection in clinical practice
- The POST-R measure provides rankings that can inform decision-making more efficiently
- The implementation of the method in Stata is in progress
- It is important that a clear and transparent description of the criteria to be used for the definition of $\mathbf{Q}^{(\mathbf{0})}$ and z are available in the protocol.
- Our method may target primarily network meta-analyses stating *"more well-conducted studies are necessary"*