Multiple-Treatments **M**eta-**A**nalysis

A framework for evaluating and ranking multiple health technologies

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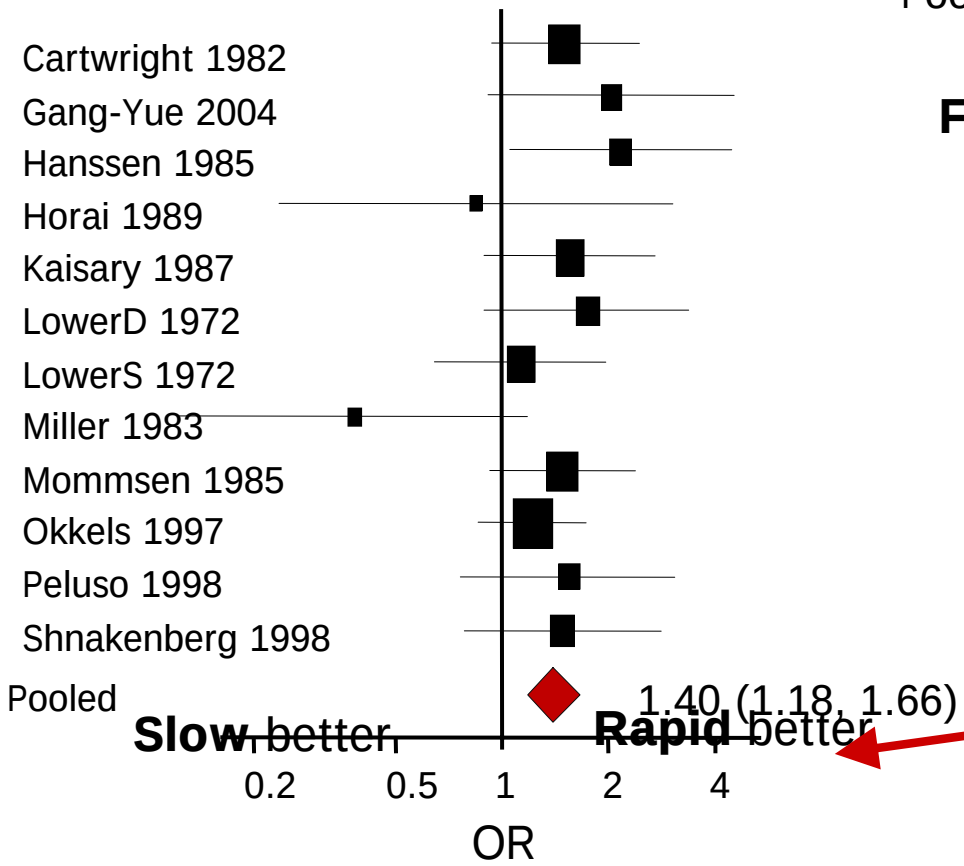
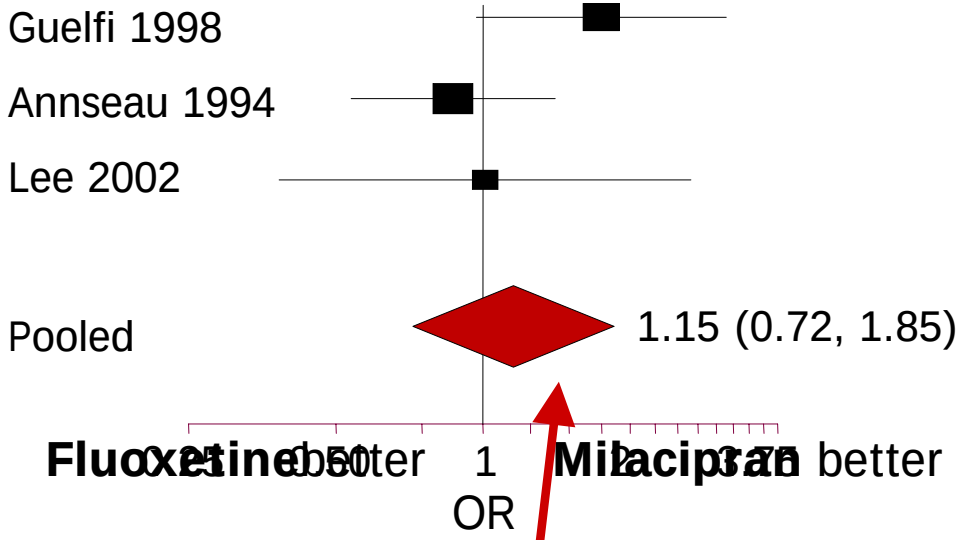
Meta-analysis comparing **two** NAT2 genotypes (slow vs rapid) in bladder cancer risk



Estimates with 95% confidence intervals



Meta-analysis comparing **two** antidepressants

Meta-analysis

Results of experiments or observations

- Studies usually **compare outcomes between groups**
  - The risk of TB with and without the vaccination
  - The mean weight loss with two different diets
- We can compare the outcomes between the interventions using various ways= effect sizes

Continuous data:

Mean Difference (MD): 2 kgr

	Mean weight loss	N
D1	**5kgr**	100
D2	**3kgr**	100

Binary data:

Risk of TB with BCG: 10%

Odds of TB with BCG: 1/9

	TB+	TB-	
BCG+	**10**	**90**	100
BCG-	**14**	**86**	100
	24	189	200

Relative measures

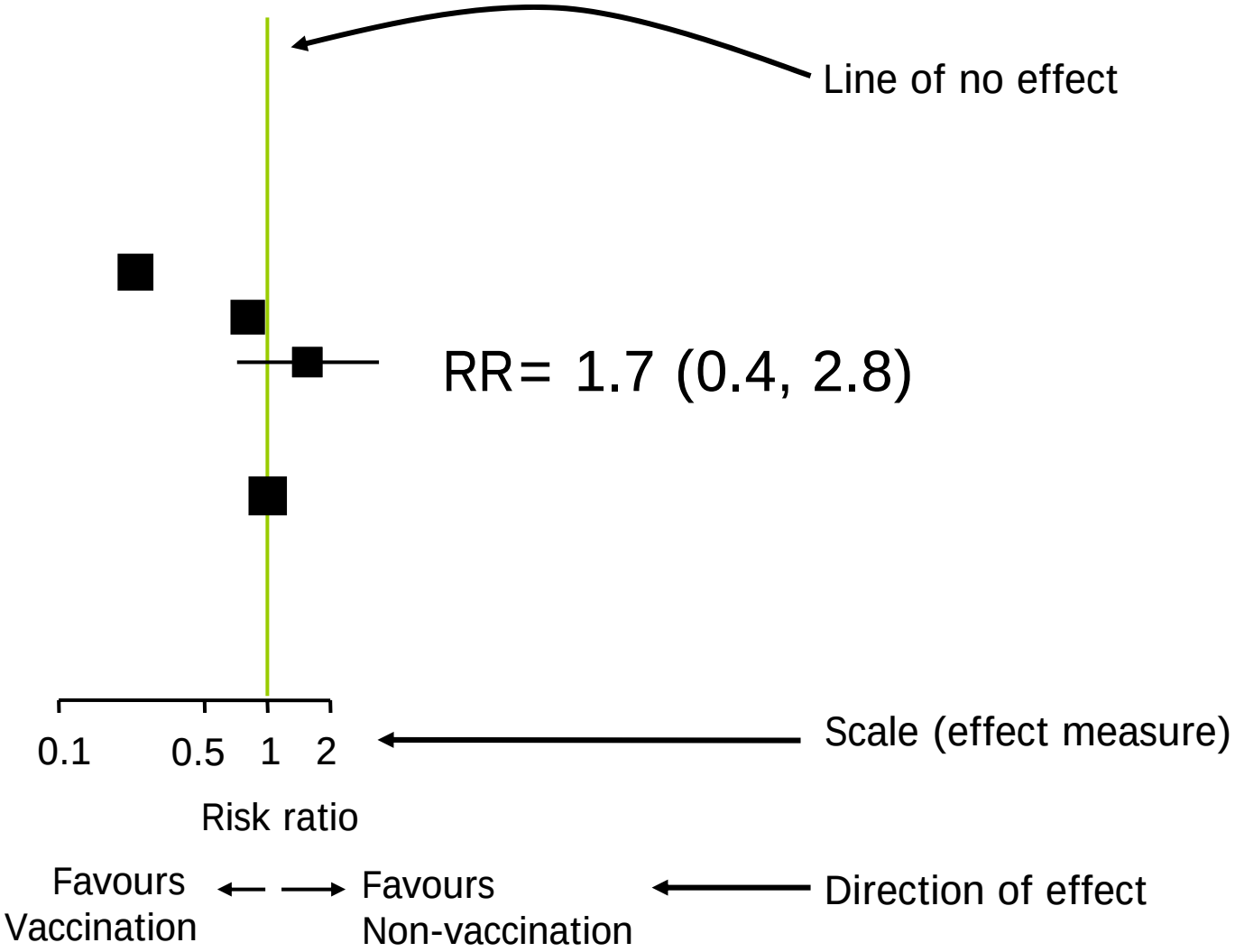
Absolute measure

$$RR = \frac{\frac{10}{100}}{\frac{14}{100}} = 0.71 = 71\% \qquad OR = \frac{\frac{10}{90}}{\frac{14}{86}} = 0.68 \qquad RD = \frac{10}{100} - \frac{14}{100} = -4\%$$

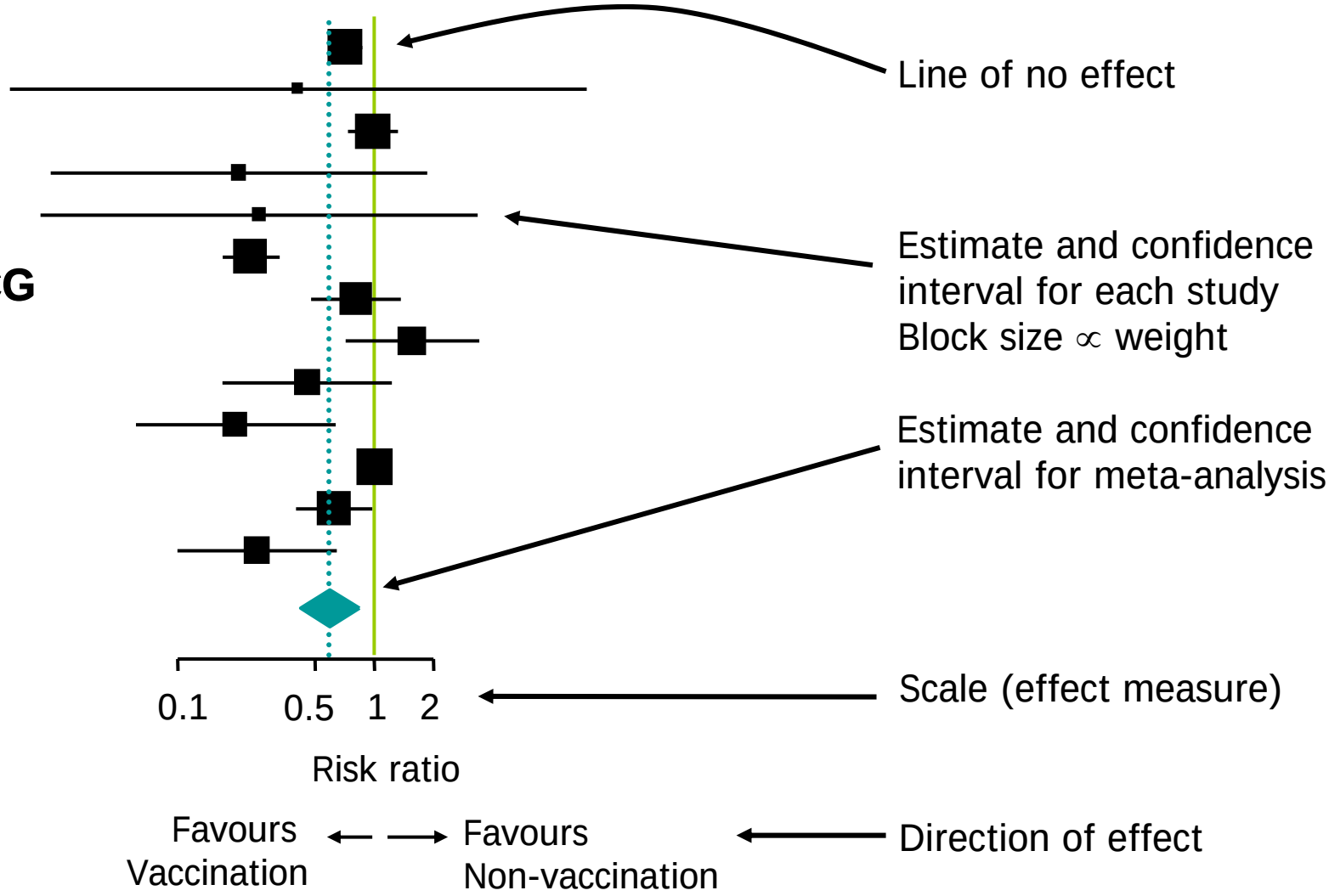
In the calculations we use lnOR and ln RR

Many studies addressing the same question

Does BCG vaccine prevent TB?



Meta-analysis: the forest plot



Basic principles of meta-analysis

- Compare like with like
  - participants in one study are not directly compared with those in another
  - each study is analysed separately
  - summary statistics are combined to give the meta-analysis
- Weight studies according to the information they provide
  - usually by precision (inverse variance)
  - **gives more weight to larger studies…**

    … so that larger studies have more influence on the summary estimate

How to calculate the diamond

Inverse-variance weighted average

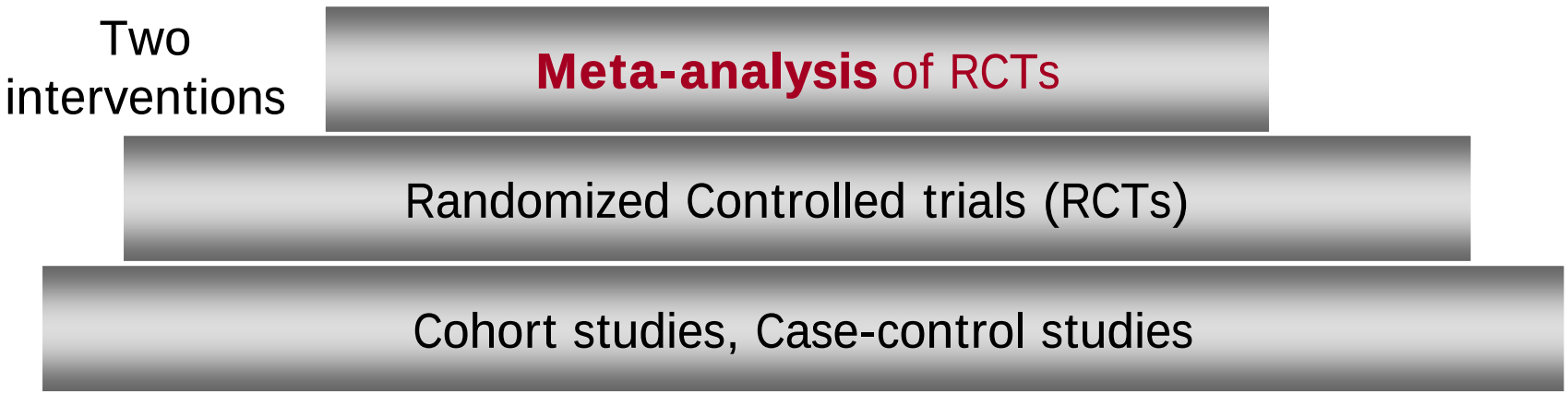
- Require from each study
  - estimate of treatment effect (e.g. RR, MD); and
  - variance of estimate
  - Weight=1/variance
- When using ratio measures, use natural log of the ratio
- Combine these using a weighted average:

$$\textbf{pooled estimate} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}}$$

$$\textbf{with variance} = \frac{1}{\text{sum of weights}}$$

Evidence Based Medicine

- Backbone: **meta-analysis**
- Rigorous statistical models
- Clinical practice guidelines
  - NICE, WHO, The Cochrane Collaboration, HuGENet



Levels of evidence For Therapy, Prevention, Aetiology and Harm

Centre for Evidence Based Medicine, University of Oxford

12 new generation antidepressants

19 **meta-analyses** published in the last two years

"Although **Mirtazapine** is likely to have a faster onset of action than **Sertraline and Paroxetine** no significant differences were observed…"

"...statistically significant differences in terms of efficacy .... between **Fluoxetine and Venlafaxine**, but the clinical meaning of these differences is uncertain..."

"...**meta-analysis** highlighted a trend in favour of **Sertraline** over other **Fluoxetine**"

"**Venlafaxine** tends to have a favorable trend in response rates compared with **duloxetine**"

Fluoxetine: 28€ Venlafaxine:111€ Sertaline: 76 €

12 new generation antidepressants

19 **meta-analyses** published in the last two years

paroxetine —— reboxetine

duloxetine —— mirtazapine

escitalopram —— fluvoxamine

milnacipran —— citalopram

sertraline —— venlafaxine

bupropion —— fluoxetine

milnacipran —— paroxetine

sertraline ? duloxetine

bupropion —— escitalopram

fluvoxamine —— milnacipran

12 new generation antidepressants

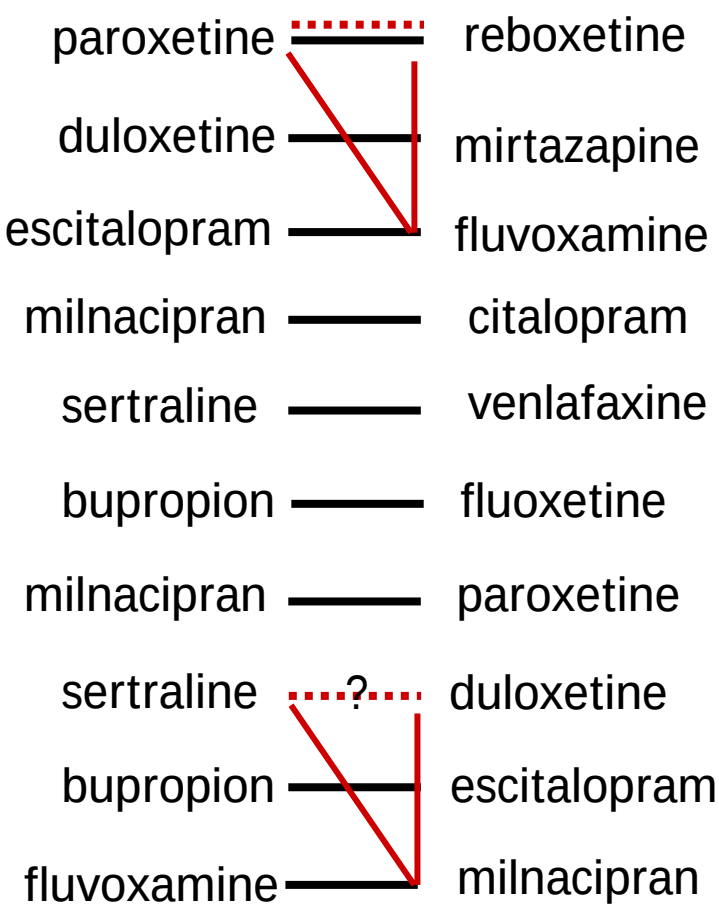
19 **meta-analyses** published in the last two years

paroxetine	—	reboxetine
duloxetine	—	mirtazapine
escitalopram	—	fluvoxamine
milnacipran	—	citalopram
sertraline	—	venlafaxine
bupropion	—	fluoxetine
milnacipran	—	paroxetine
sertraline	?	duloxetine
bupropion	—	escitalopram
fluvoxamine	—	milnacipran

	Probability to be the best
paroxetine	0%
sertraline	7%
citalopram	0%
escitalopram	26%
fluoxetine	0%
fluvoxamine	0%
milnacipran	1%
venlafaxine	11%
reboxetine	0%
bupropion	0%
mirtazapine	54%
duloxetine	0%

12 new generation antidepressants

19 **meta-analyses** published in the last two years



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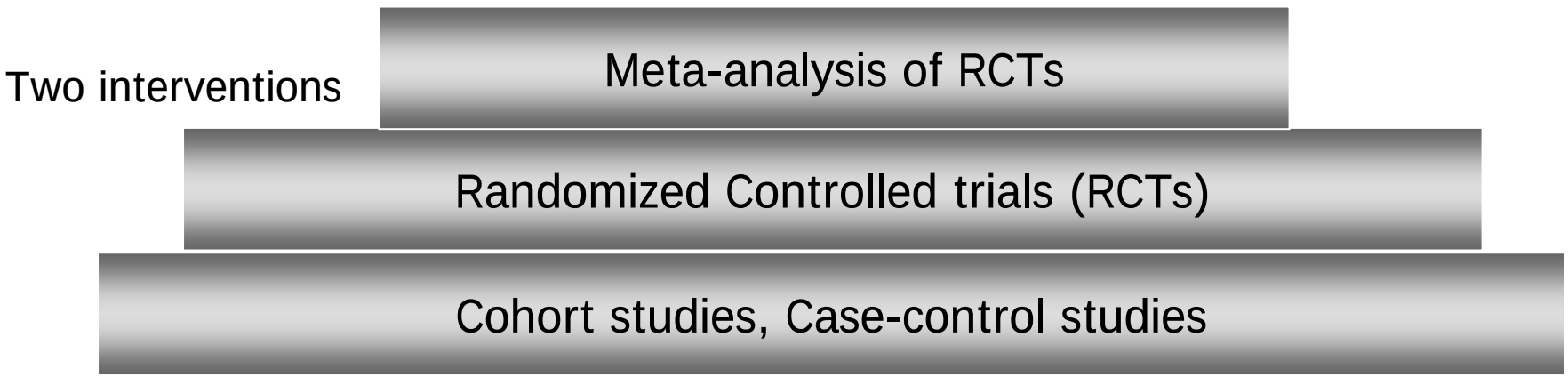
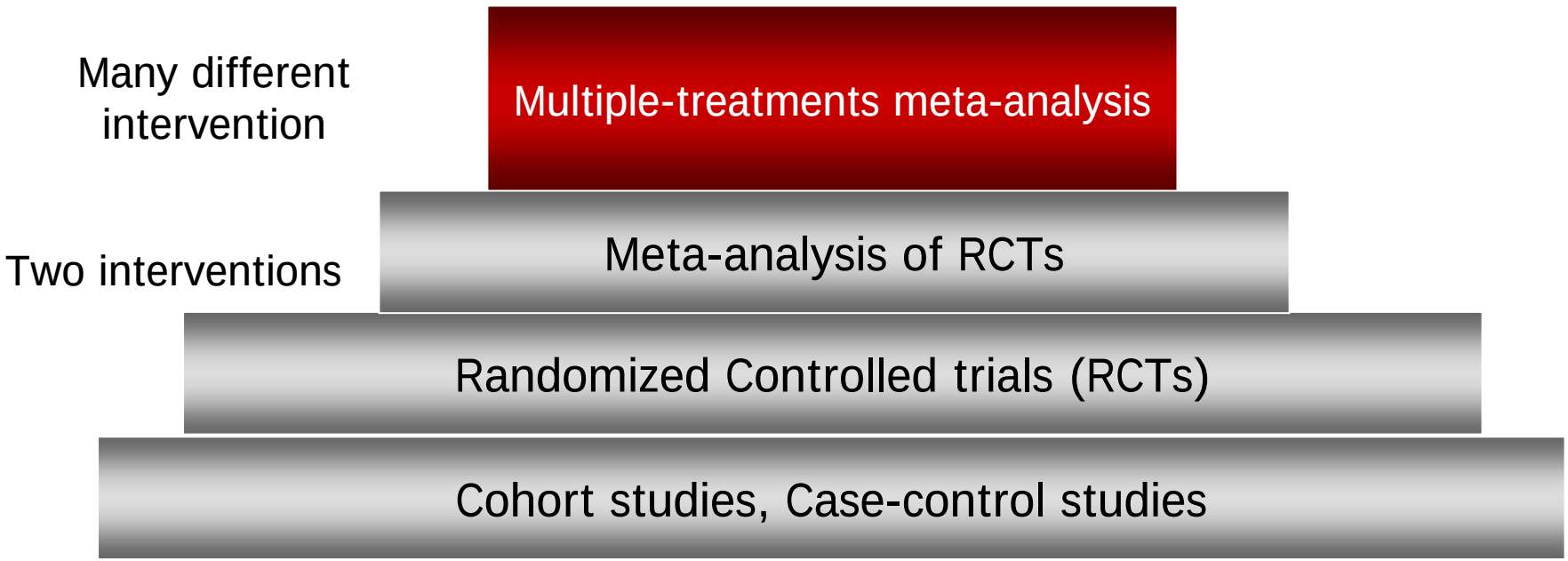
milnacipran	1%
venlafaxine	11%
reboxetine	0%
bupropion	0%
mirtazapine	54%
duloxetine	0%

Current meta-analysis misses data!

A new methodological framework



A new methodological framework



l,j,k random treatments

y_i the outcome of experiment i

θ_t the random effect

$$\begin{pmatrix} y_{1,l_1,j_1} \\ y_{2,l_2,j_2} \\ \vdots \\ y_{N,l_N,j_N} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_{1,l_1,j_1} \\ \theta_{2,l_2,j_2} \\ \vdots \\ \theta_{N,l_N,j_N} \end{pmatrix}, \Sigma \right)$$

Likelihood

$$\begin{pmatrix} \theta_{1,l_1,j_1} \\ \theta_{2,l_2,j_2} \\ \vdots \\ \theta_{N,l_N,j_N} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{1,l_1,j_1} \\ \mu_{2,l_2,j_2} \\ \vdots \\ \mu_{N,l_N,j_N} \end{pmatrix}, \begin{bmatrix} \tau_1^2 & c & c & c \\ c & \tau_2^2 & c & c \\ \vdots & \vdots & \ddots & \vdots \\ c & c & c & \tau_N^2 \end{bmatrix} \right)$$

Random effects

$$\mu_{lj} = \mu_{lk} + \mu_{kj}$$

Consistency equations

Winbugs Code

Likelihood

```
model{
for(i in 1:NHtH){delta[i]~dnorm(mean[i],precision )}
delta[(NHtH+1):N]~dmnorm(mean[(NHtH+1):N],K[,])
for(i in 1:(N-NHtH)){for(j in 1:(N-NHtH)){
K[i,j]<-precision*H[i,j]}}
```

Random effects

```
for(i in 1:N){mean[i] <- d[t[i]] - d[b[i]] }
for (k in 1:NT)  {d[k] ~ dnorm(0,.0001) }
for (c in 1:(NT-1)) {  for (k in (c+1):NT)
{ mean[c,k] <- d[k] - d[c]
 OR[c,k] <- exp(mean[c,k] )}}
```

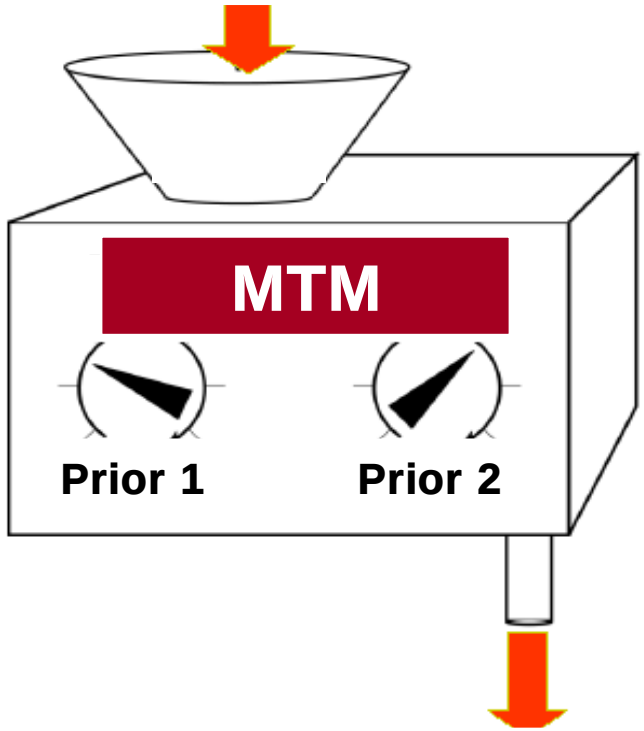
Consistency equations

```
precision<-1/pow(sd,2)
sd~dnorm(0,1)I(0,)}
```

Priors

MTM

Experiments



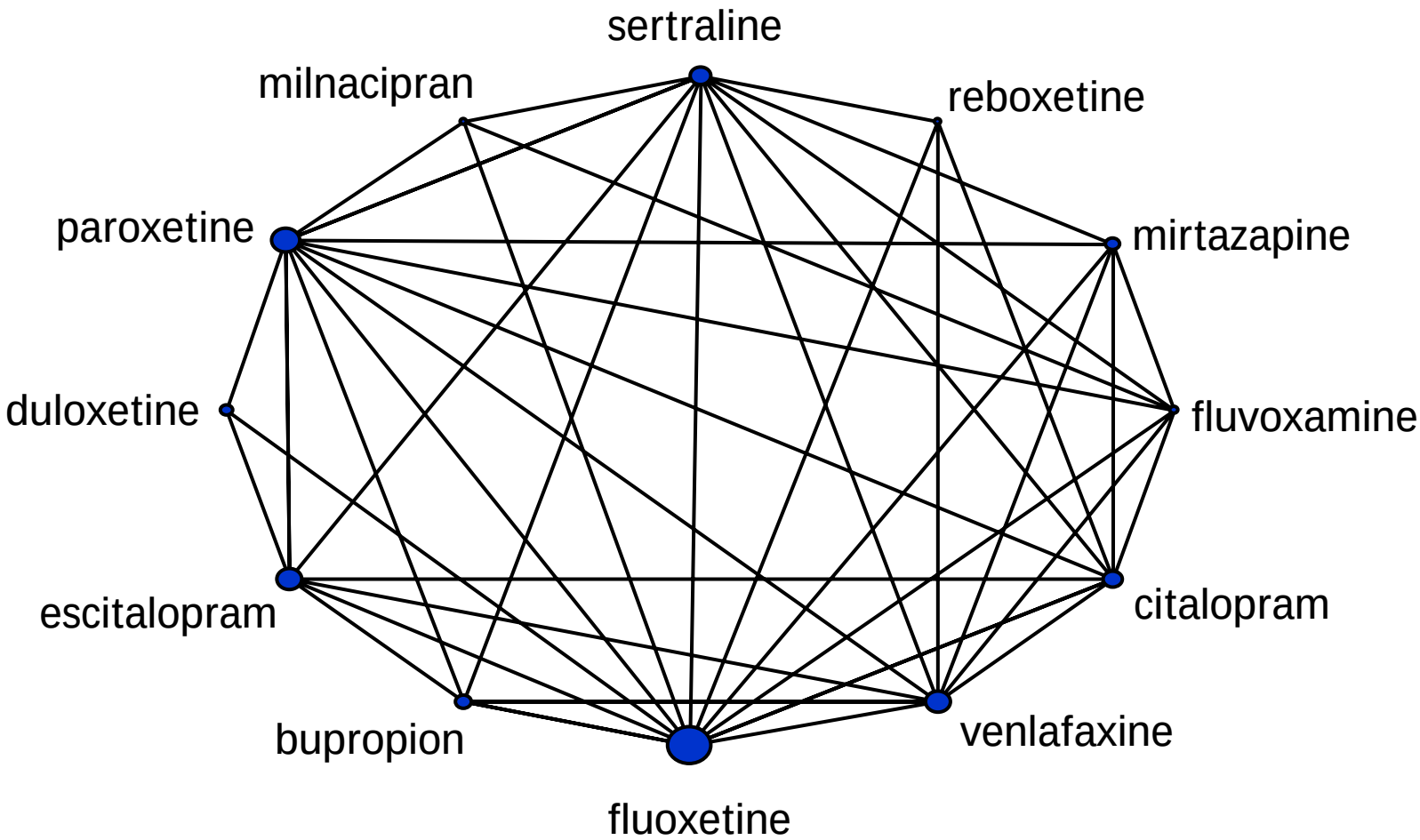
Ranking of all available health technologies

Today you will learn…

The idea of indirect comparison
The conceptual principals of MTM
Simple example with basic statistics..... (OMG!)
The result of an MTM analysis
The notion of inconsistency and its sources
The assumptions of MTM analysis

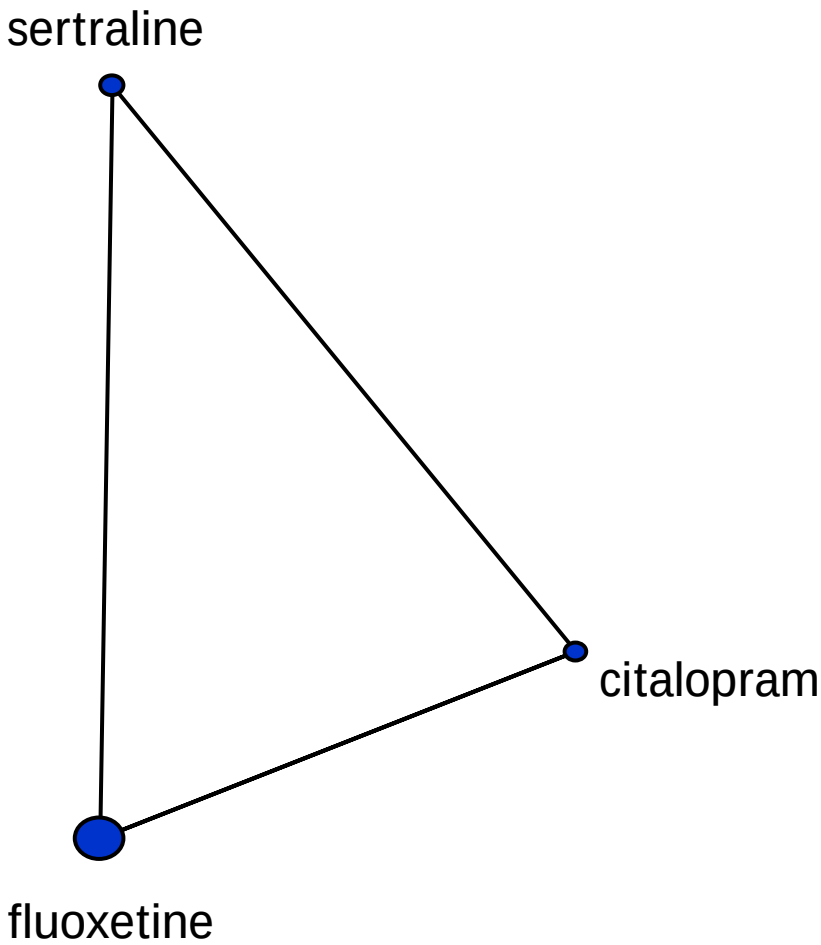
(but not how to fit the model itself!)

Network of experimental comparisons



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

Network of experimental comparisons



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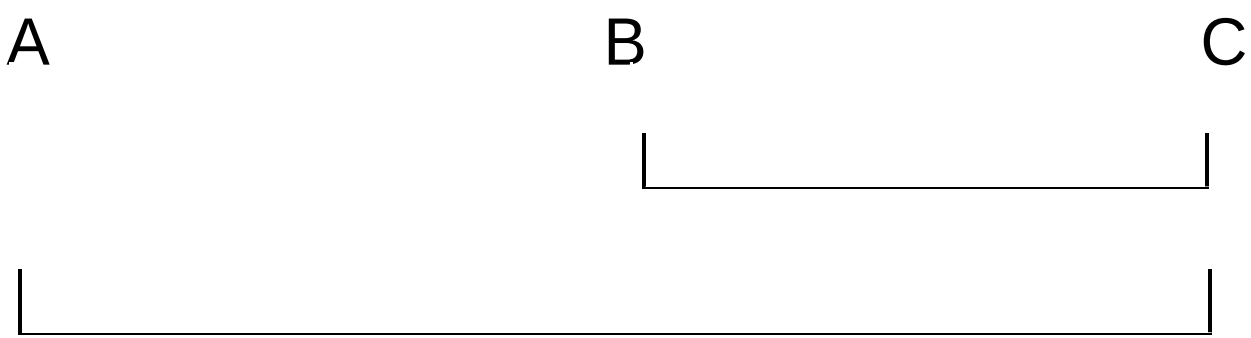
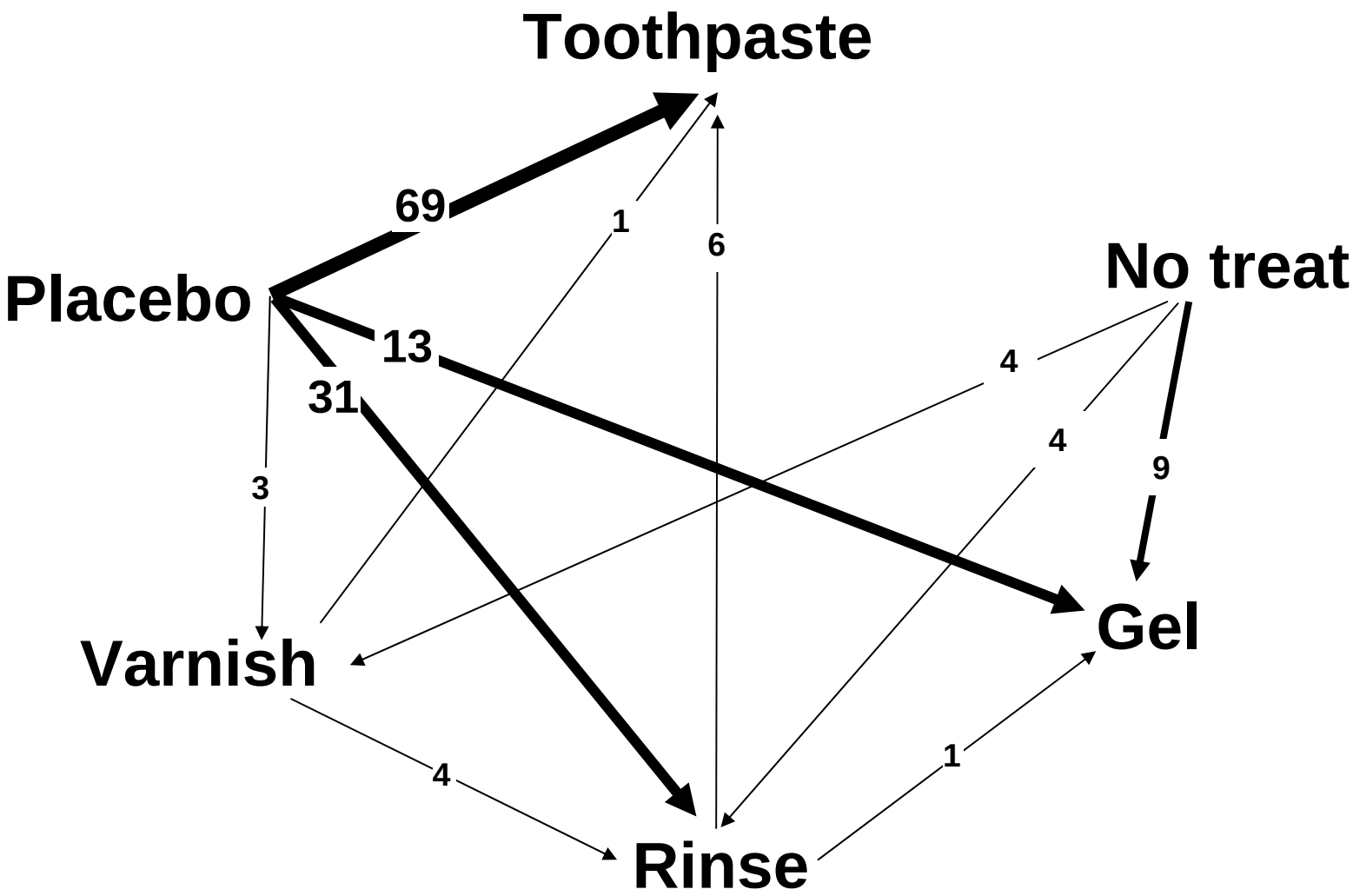
Indirect comparison

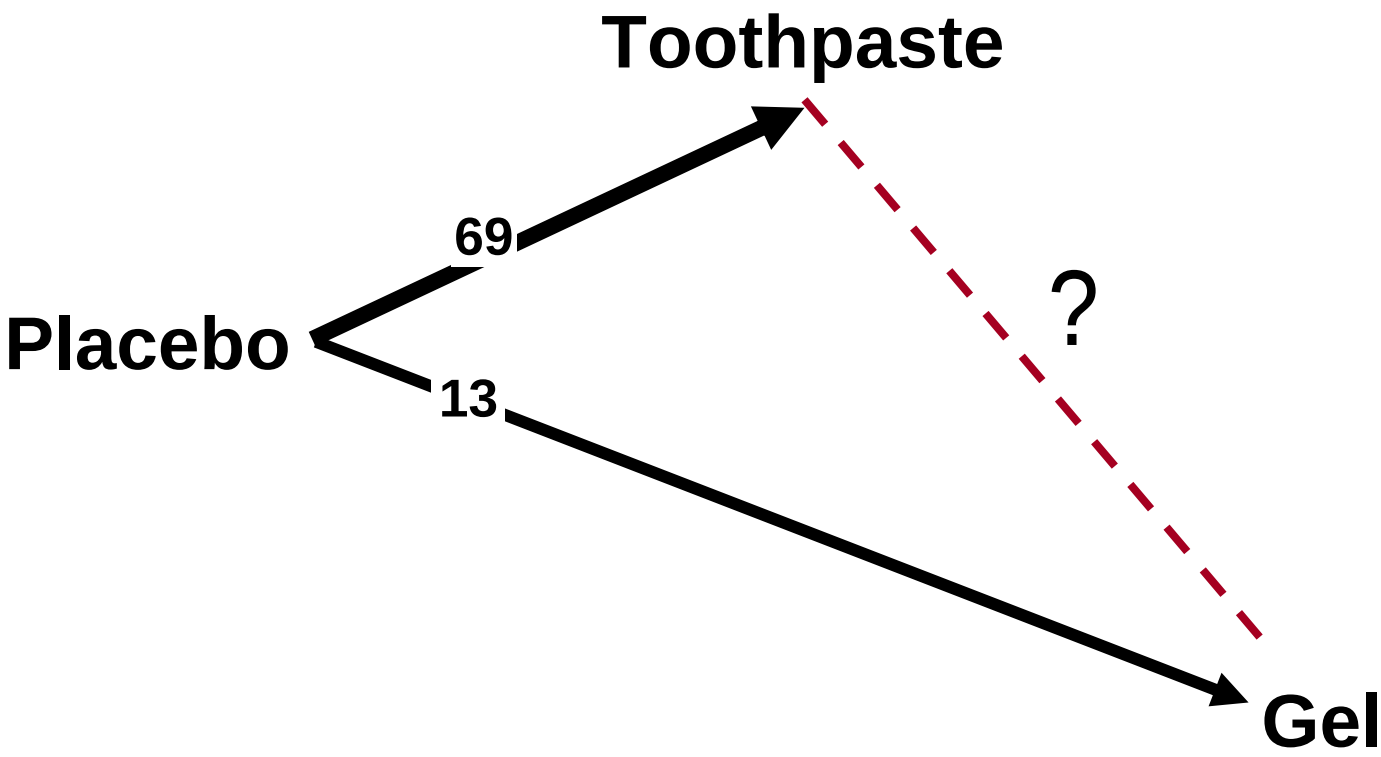
- We can obtain an *indirect* estimate for A vs B from RCTs comparing A vs C and B vs C:



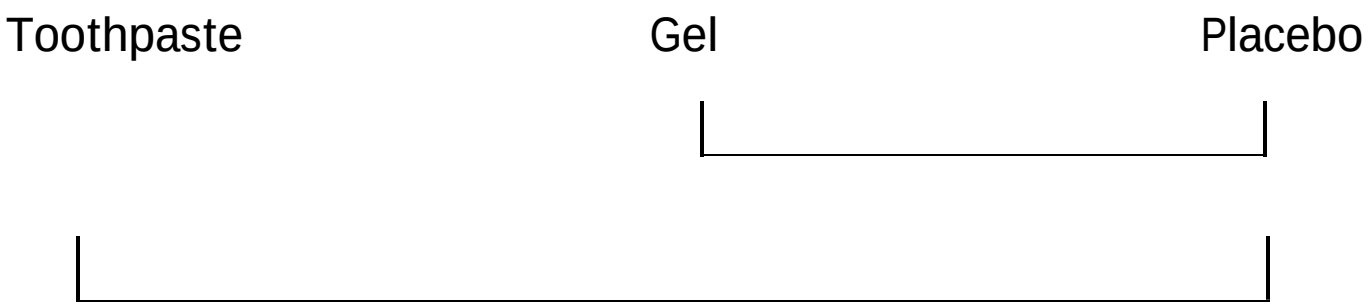
$$MD_{AB} = MD_{AC} - MD_{BC}$$

$$Var(MD_{AB}) = Var(MD_{AC}) + Var(MD_{BC})$$


Toothpaste
69
1
6
Placebo
No treat
13
4
31
4
9
3
Gel
Varnish
4
1
Rinse


Toothpaste
69
?
Placebo
13
Gel

Simple exercise: prevented mean caries



Comparison	MD	CIs
Placebo vs Toothpaste	-0.34	(-0.41, -0.28)
Placebo vs Gel	-0.19	(-0.30, -0.10)

How to compare Gel to Toothpaste?

Estimate indirect MD and a 95% CI

Flash back to stats…

Each estimate has uncertainty as conveyed by the variance, the standard error and the 95% CI

Variance = SE^2

95% CI (Low CI, High CI): x-1.96·SE to x+1.96·SE :

SE = (High CI – Low CI) / 3.92

Pen and paper (and calculator!) exercise!

Indirect MD_{GvsT} = $MD_{PvsT} - MD_{PvsG}$

Indirect MD_{GvsT} = -0.34 – (-0.19)= -0.15

Variance Indirect MD_{GvsT} = Variance MD_{PvsT} + Variance MD_{PvsG}

Variance MD_{PvsT} = ((high CI –low CI)/3.92)^2

Variance MD_{PvsT}= ((-0.28– (-0.41))/3.92)^2 =0.0011

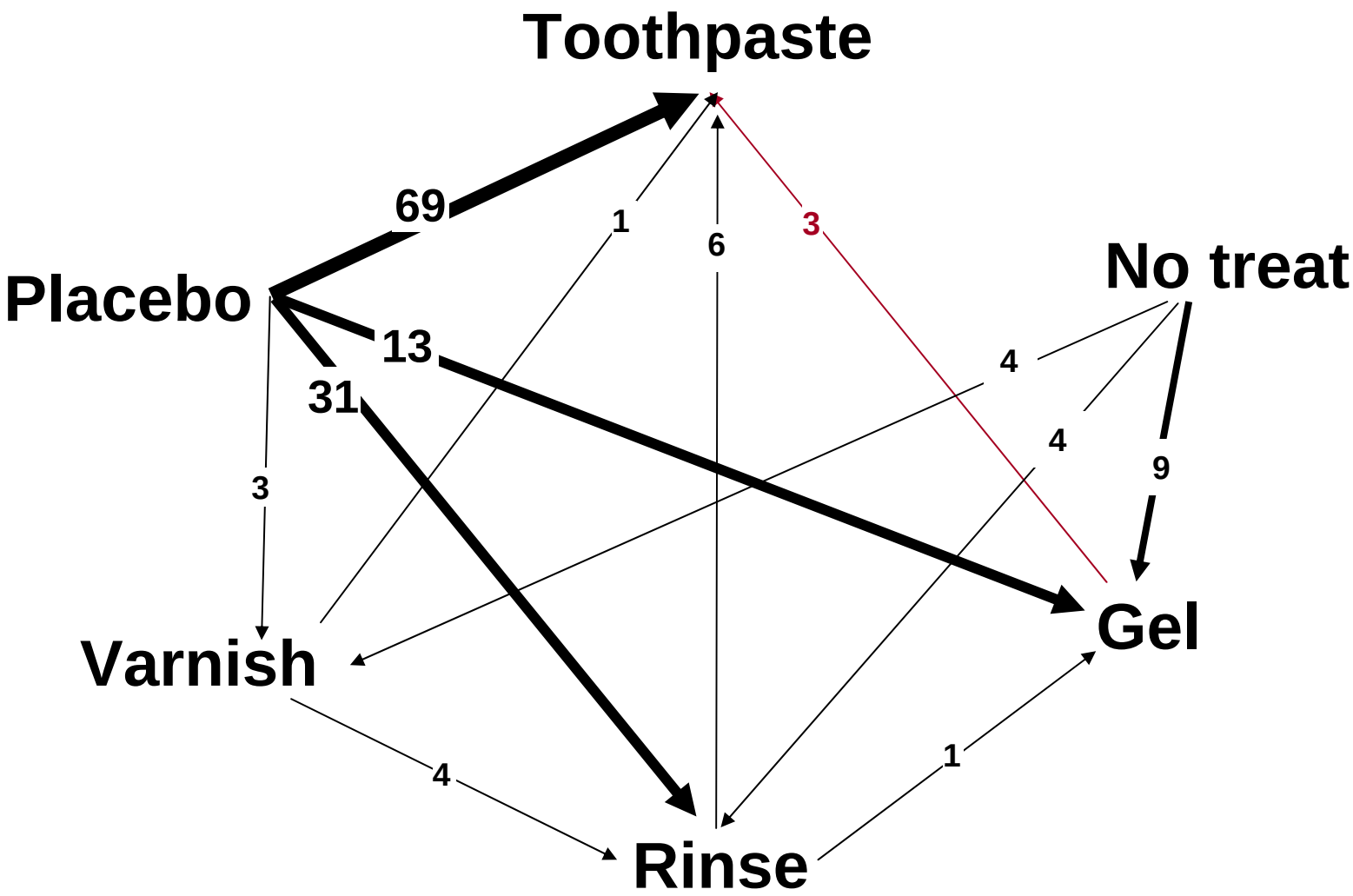
Variance MD_{GvsT}= ((-0.10– (-0.30))/3.92)^2 =0.0026

Variance Indirect MD_{GvsT} = 0.0011+0.0026=0.0037

SE Indirect MD_{GvsT} = sqrt(0.0037)=0.061

95% CI for Indirect MD_{GvsT} = (-0.15 – 1.96·0.061, -0.15 + 1.96·0.061)

95% CI for Indirect MD_{GvsT} = (-0.27, -0.03)


Toothpaste
69
1
6
3
No treat
Placebo
13
4
31
4
3
9
Gel
Varnish
4
1
Rinse

Combining direct and indirect evidence

- Inverse variance method
- Each estimate is ‘weighted’ by the inverse of the variance
- Then a common (pooled) result is obtained!

$$\text{pooled MD} = \frac{\frac{1}{\text{var}_{Direct}} MD_{Direct} + \frac{1}{\text{var}_{Indirect}} MD_{Indirect}}{\frac{1}{\text{var}_{Direct}} + \frac{1}{\text{var}_{Indirect}}}$$

$$\text{pooled MD} = \frac{\frac{1}{0.011}0.04 + \frac{-1}{0.0037}0.15}{\frac{1}{0.011} + \frac{1}{0.037}}$$

Indirect MD_{GvsT} = - 0.15

Variance Indirect MD_{GvsT} = 0.0037

Direct MD_{GvsT} = 0.04

Variance Direct MD_{GvsT} = 0.011

Pooled MD_{GvsT} = -0.14

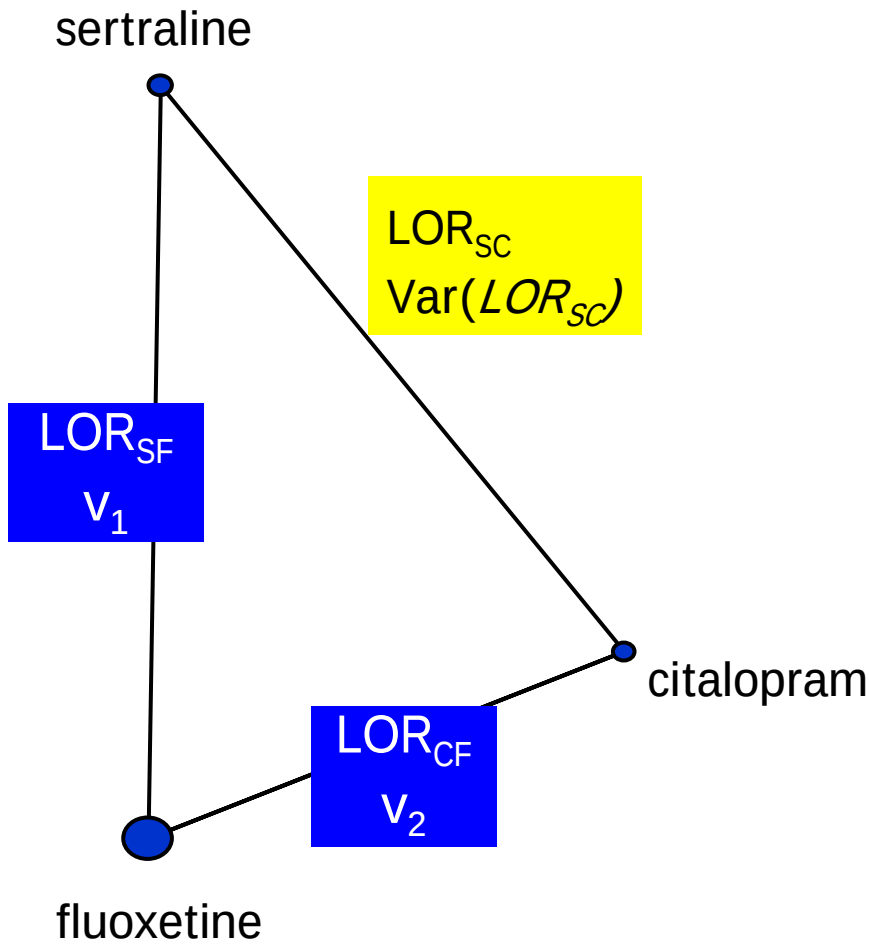
You can do this with any measure… lnOR, lnRR, RD, mean difference, HR, Peto's lnOR etc...

Network of experimental comparisons

Indirect estimation

$LOR_{SC} = LOR_{SF} - LOR_{CF}$

$Var(LOR_{SC}) = v_1 + v_2$



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

Network of experimental comparisons

Indirect estimation

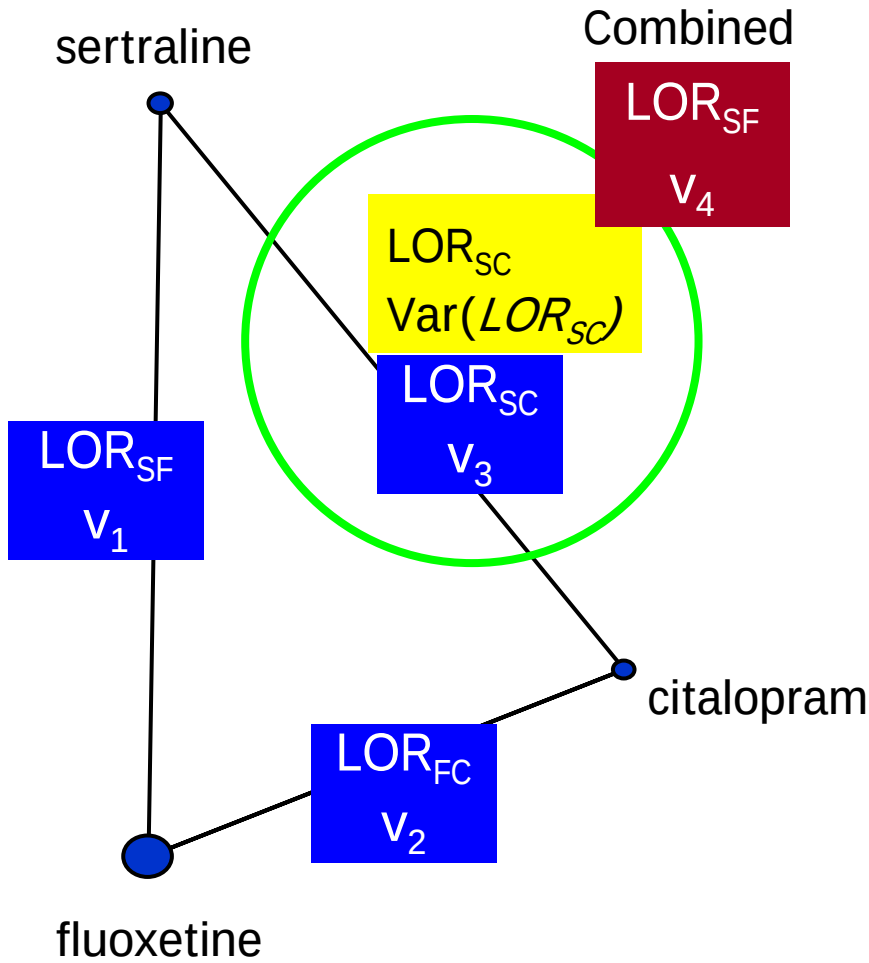
$LOR_{SC} = LOR_{SF} + LOR_{FC}$

$Var(LOR_{SC}) = v_1 + v_2$

Combine the direct estimate with the indirect estimate using IV methods

Get a combined ***LOR!***

v4<v3



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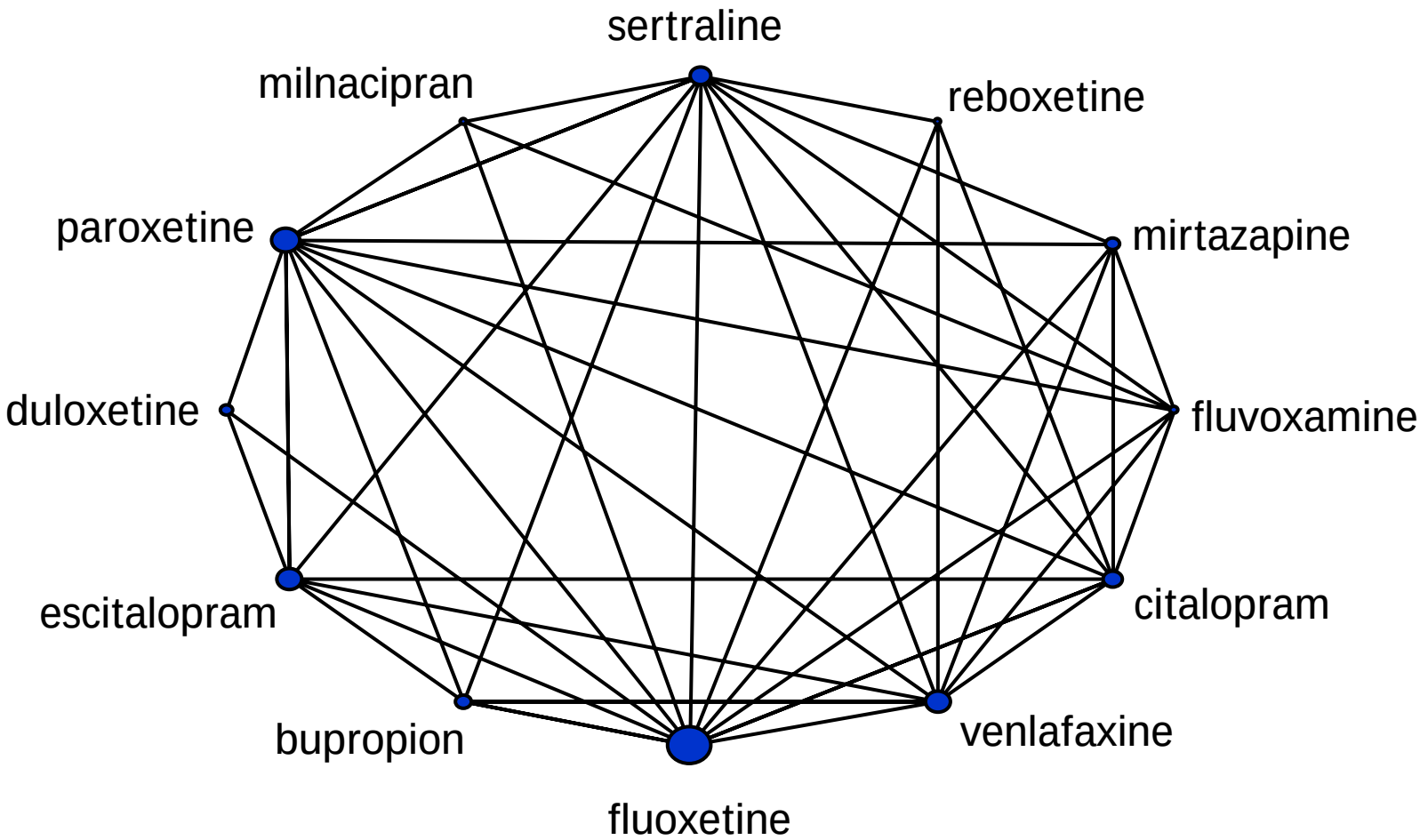
Network of experimental comparisons



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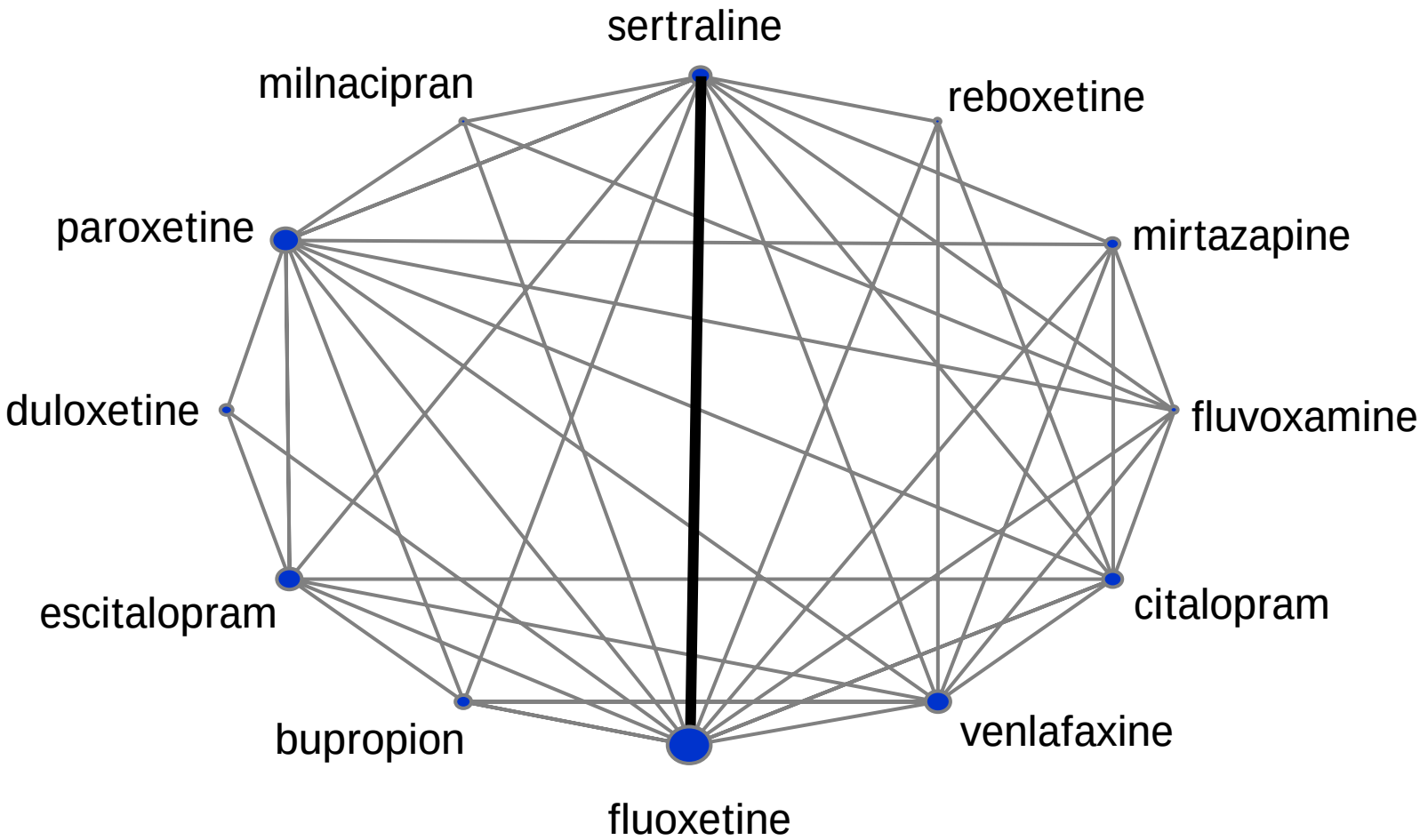

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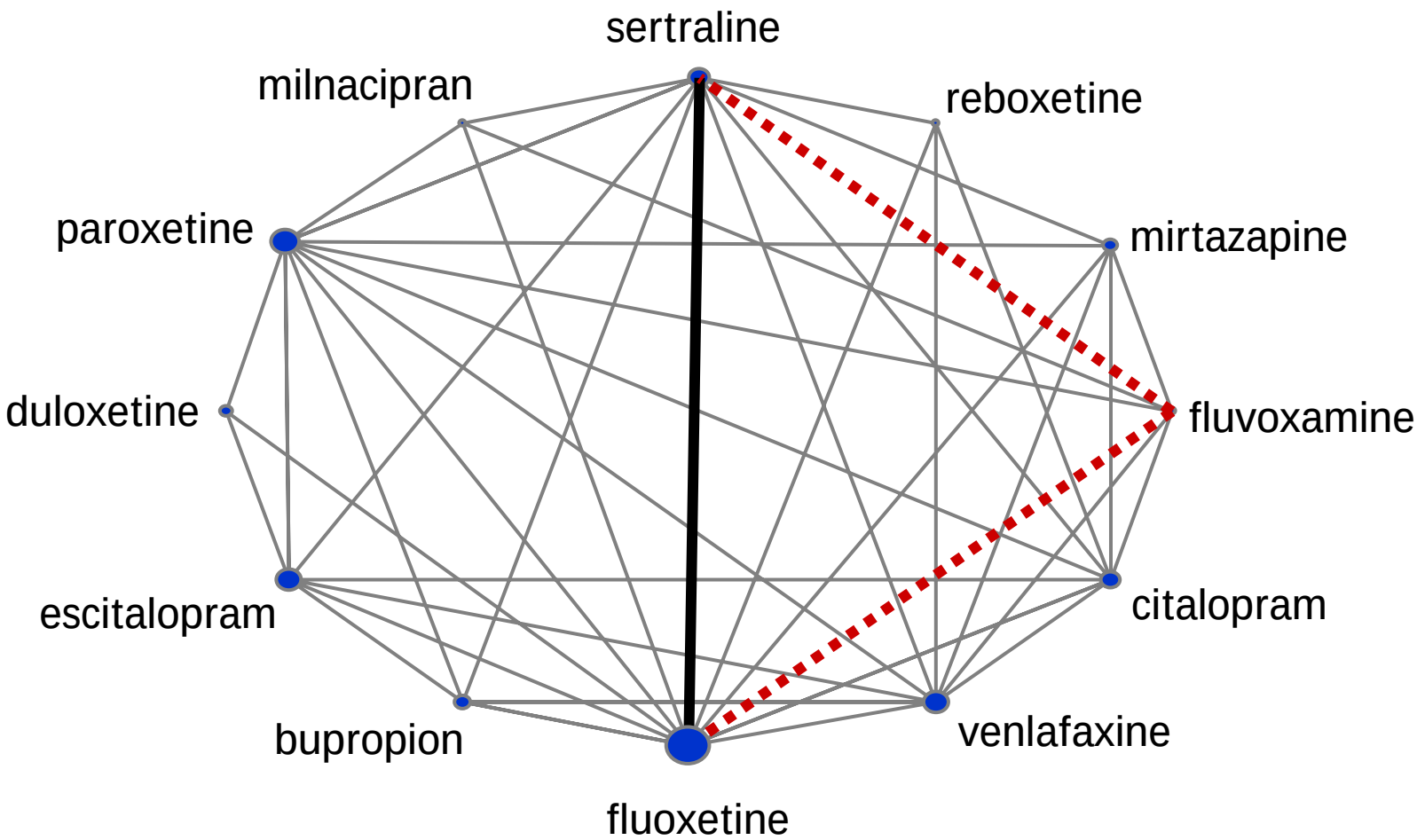

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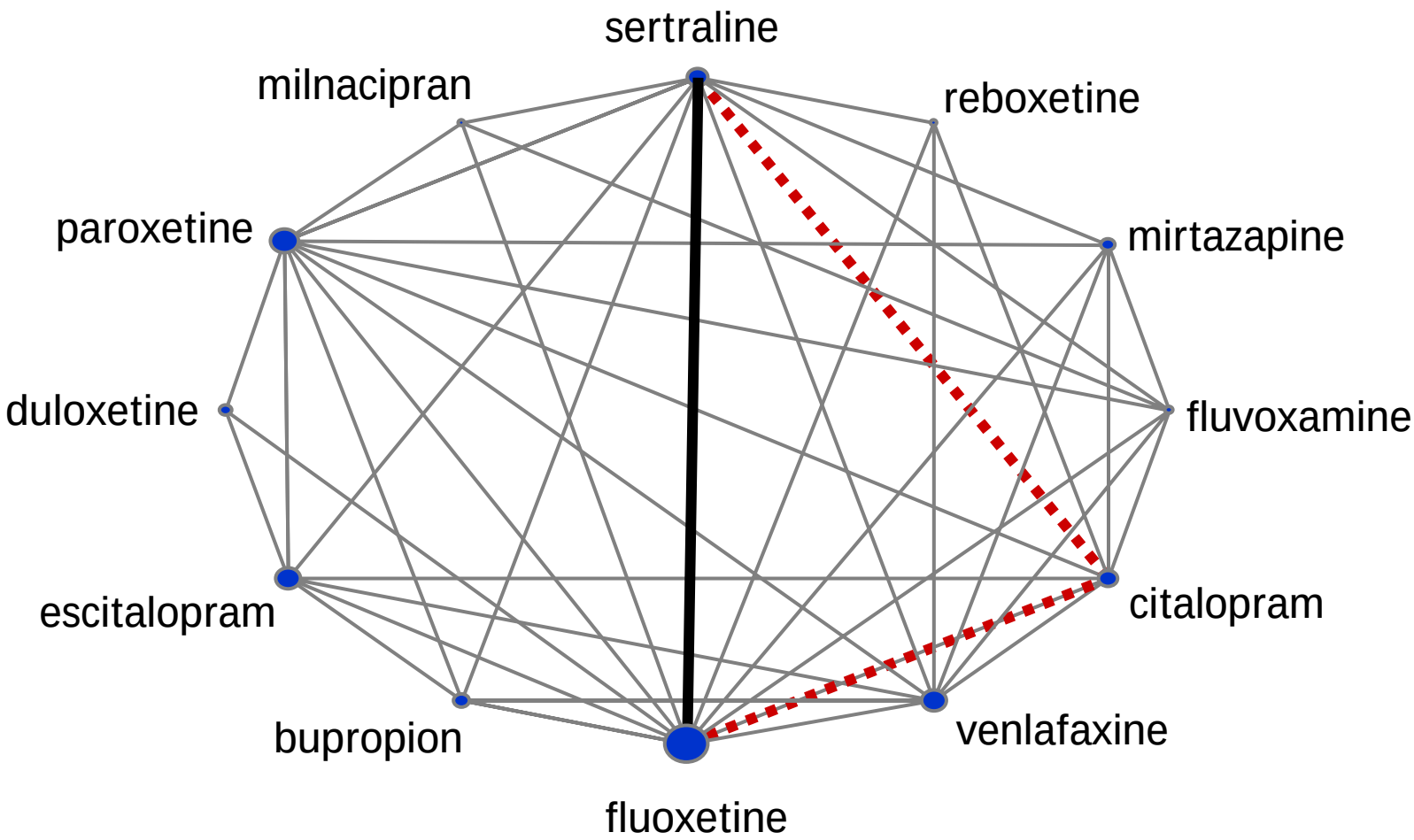

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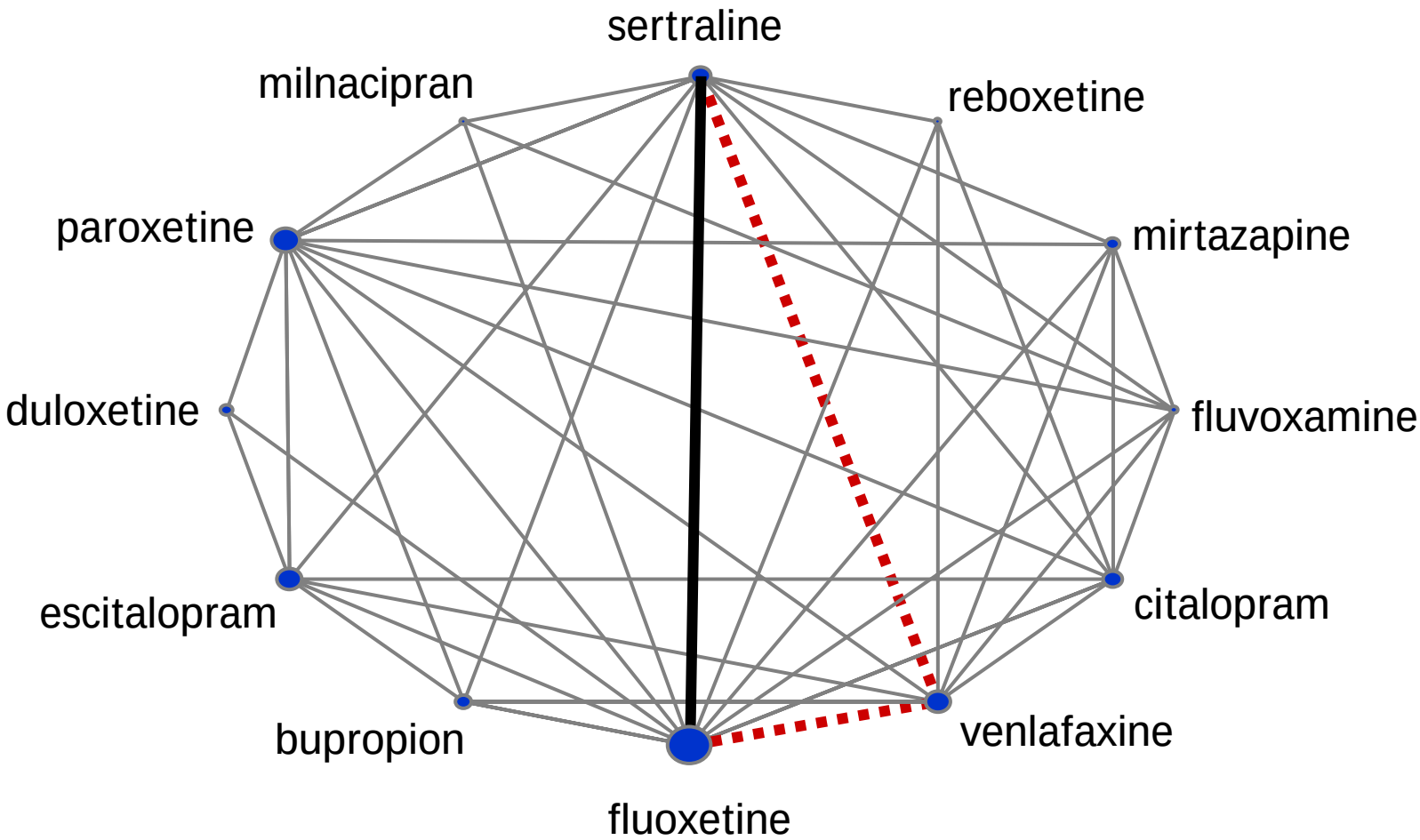

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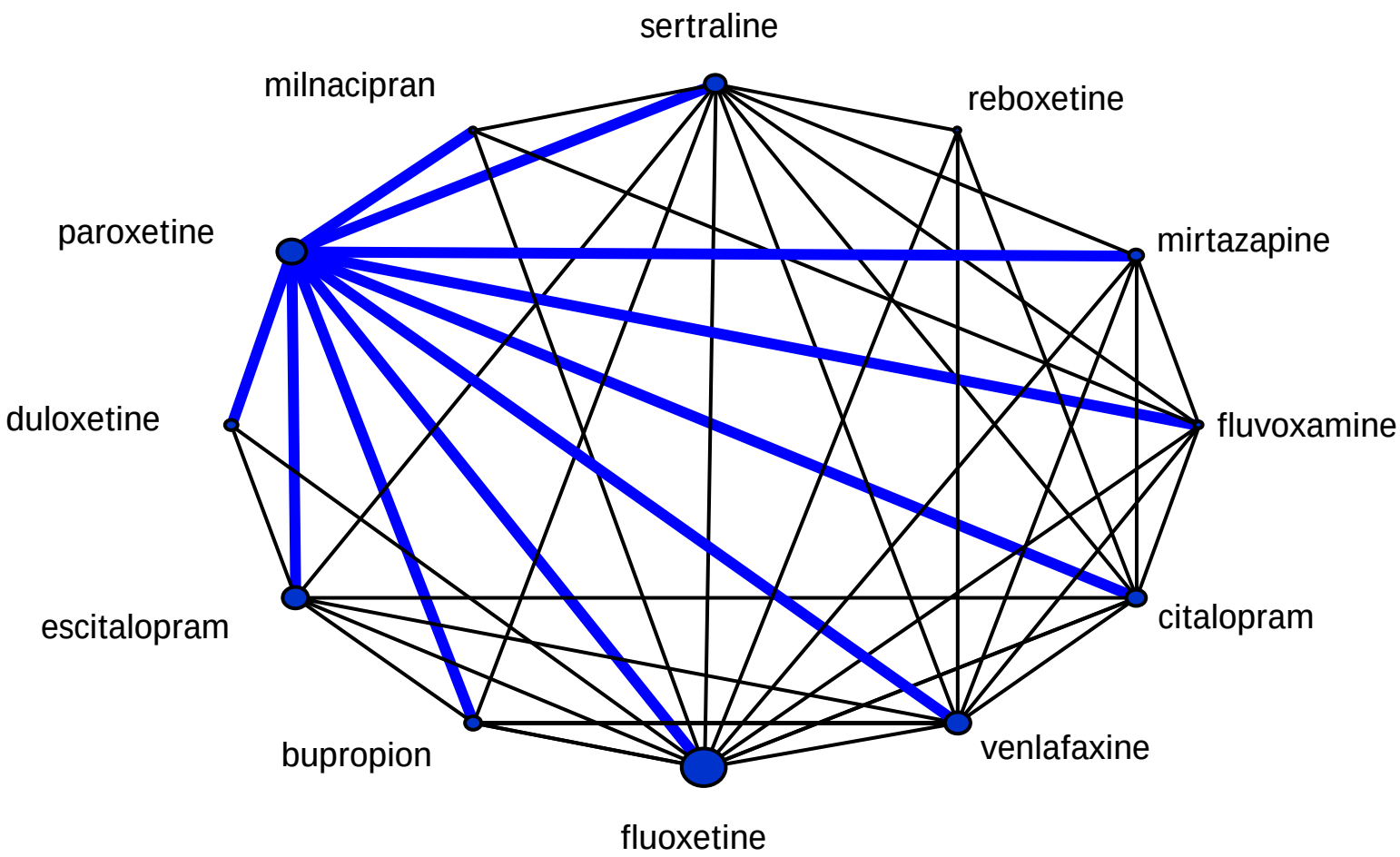
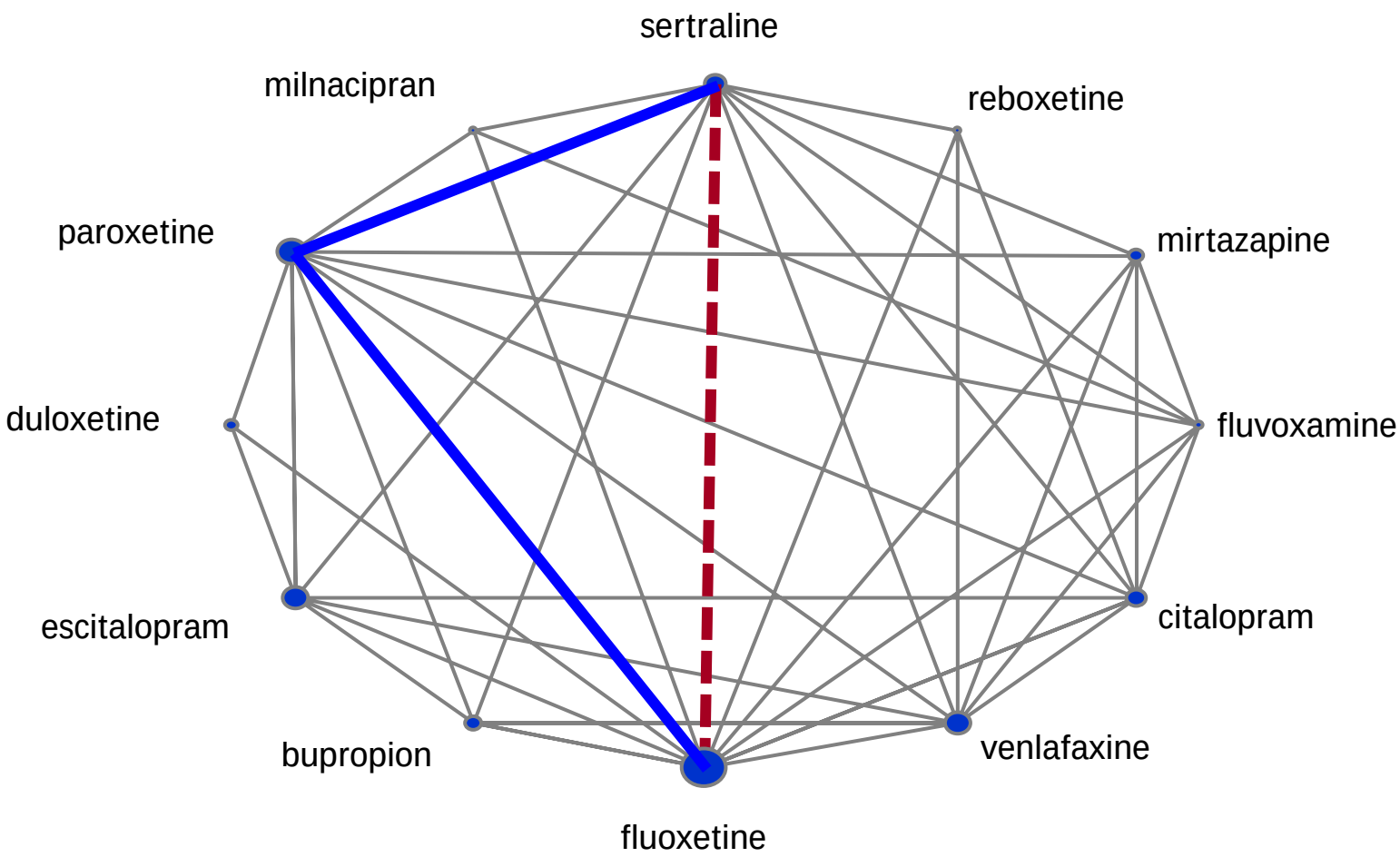
Choose basic parameters



All other contrasts are functional!



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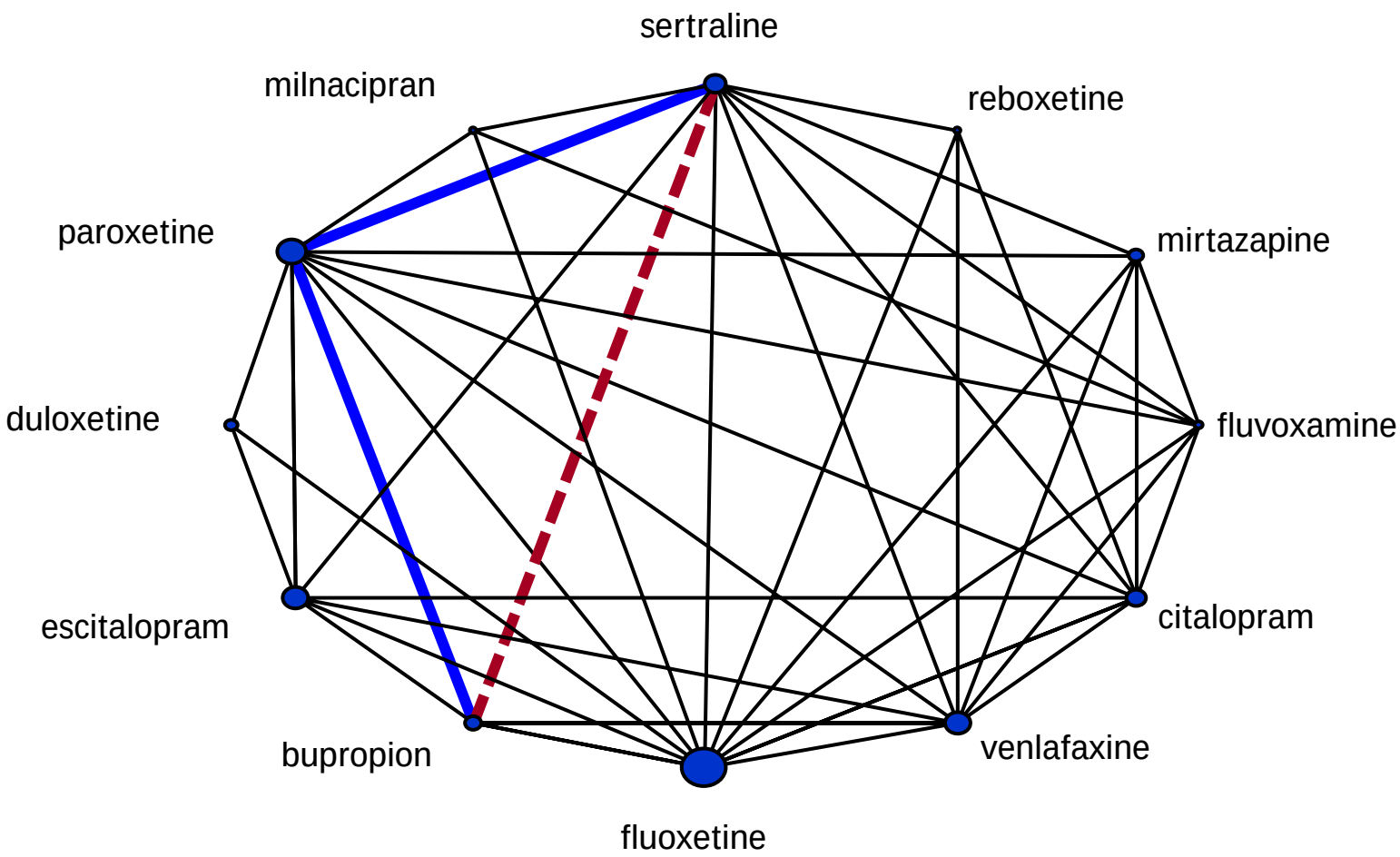

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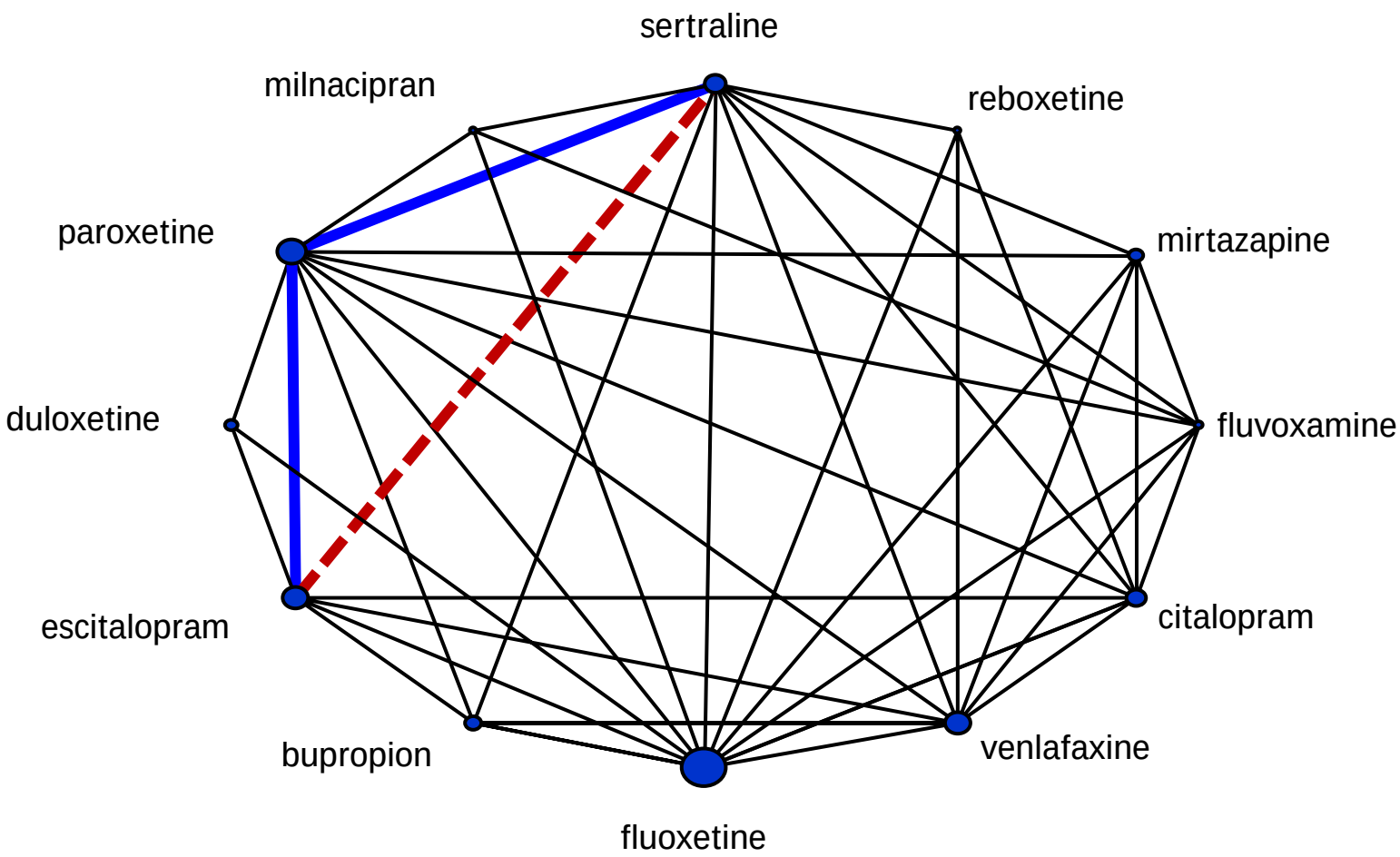
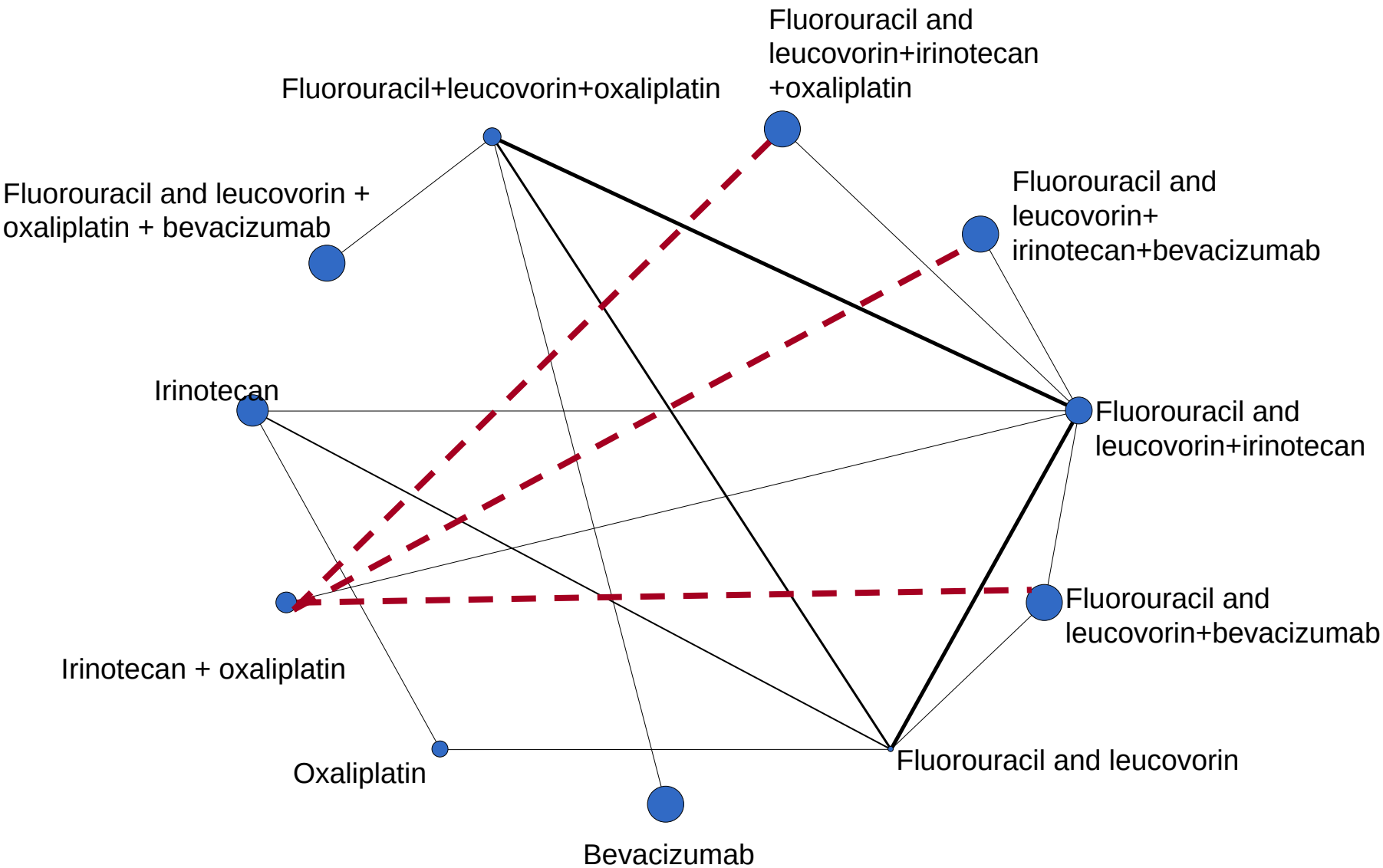


Advantages of MTM

- Ranking of many treatments for the same condition (see later)
- Comprehensive use of all available data (indirect evidence)
- Comparison of interventions which haven't been directly compared in any experiment

Colorectal Cancer

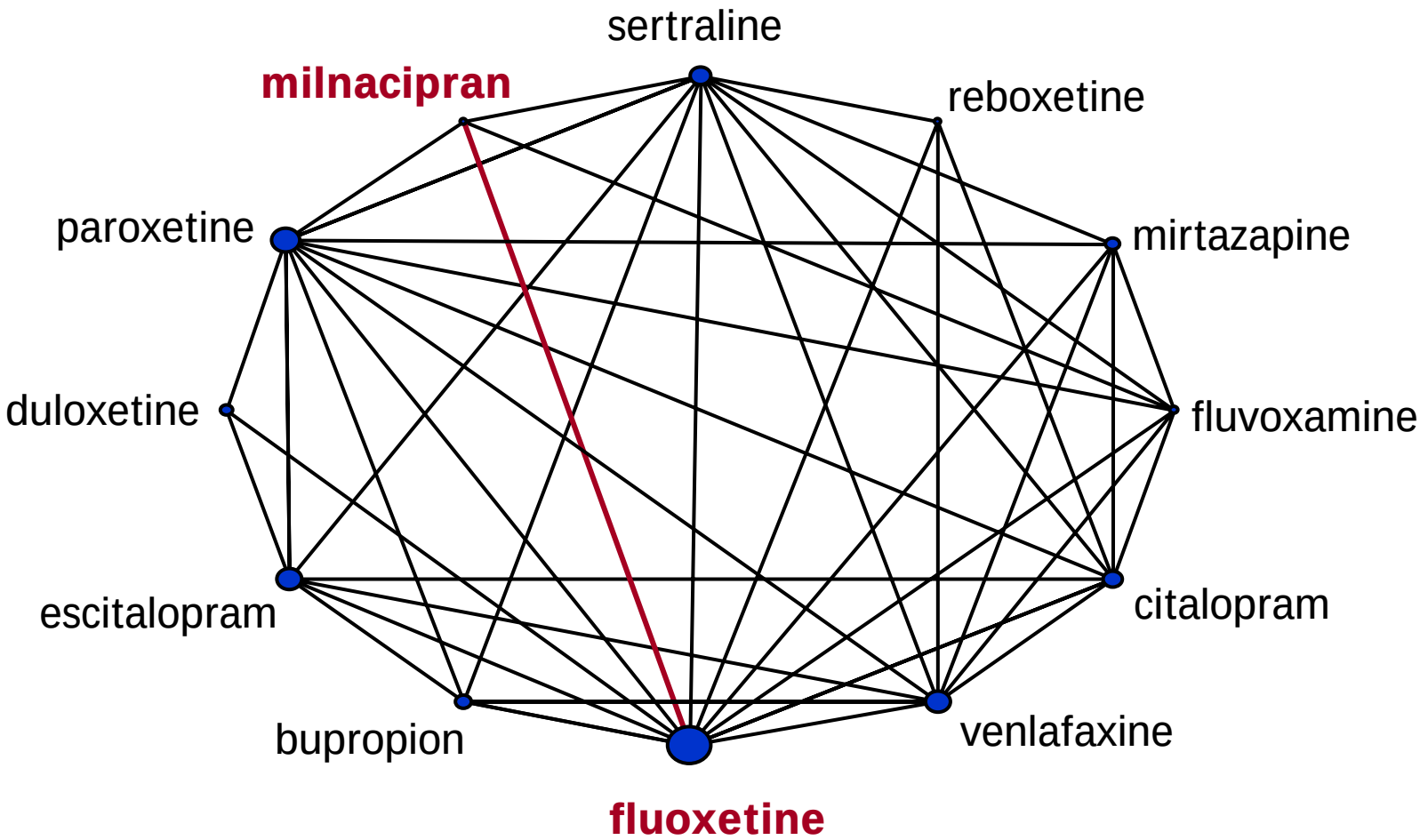


Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP: ***Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis.*** *Lancet Oncol 2007,* ***8:*** *898-911.*

Advantages of MTM

- Ranking of many treatments for the same condition (see later)
- Comprehensive use of all available data (indirect evidence)
- Comparison of interventions which haven't been directly compared in any experiment
- Improved precision for each comparison

Network of experimental comparisons



Fluoxetine vs Milnacipran (response to treatment)

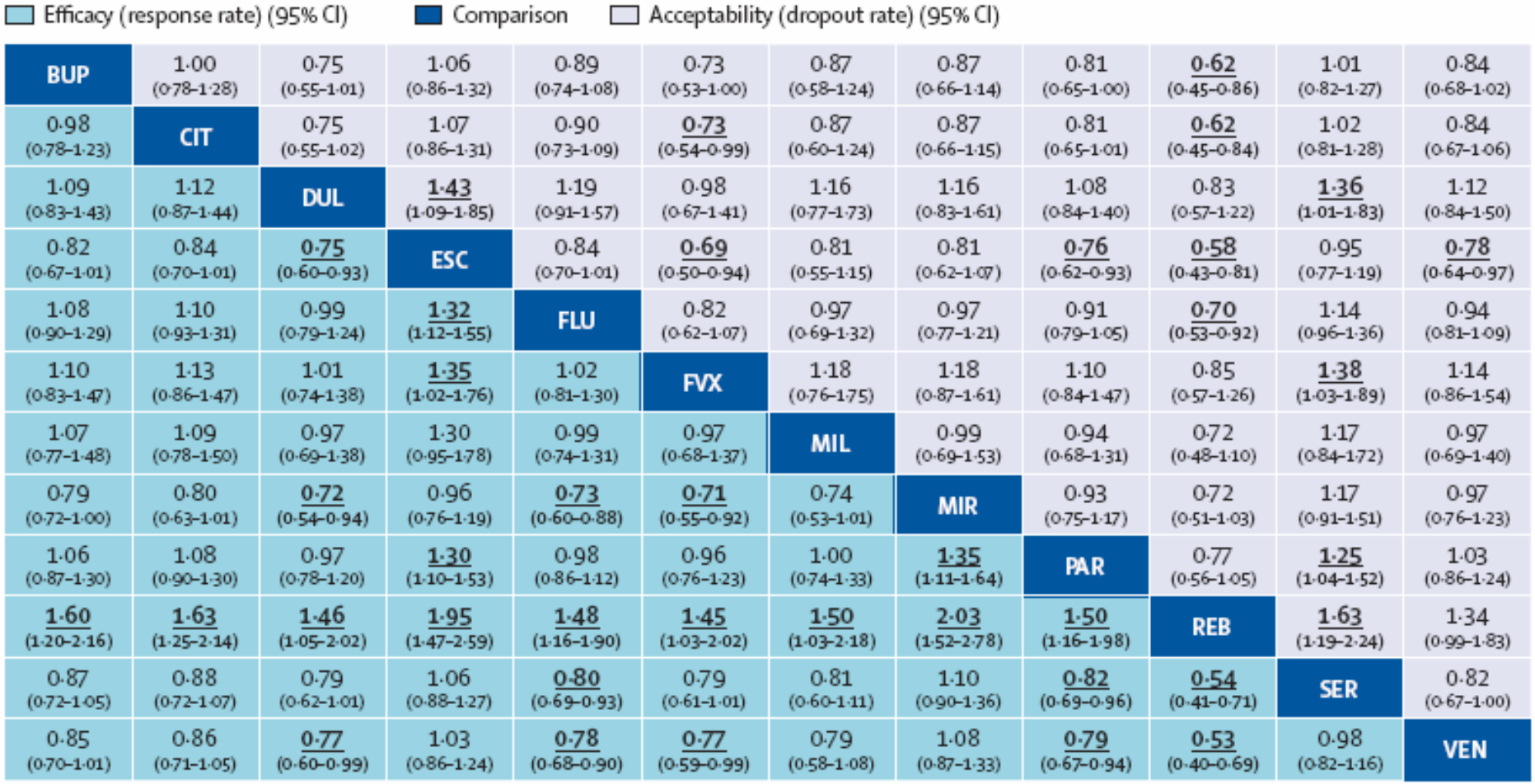
Meta-analysis: 1.15 (0.72, 1.85)

MTM: 0.97 **(0.69, 1.32)**

Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

Ranking measures from MTM

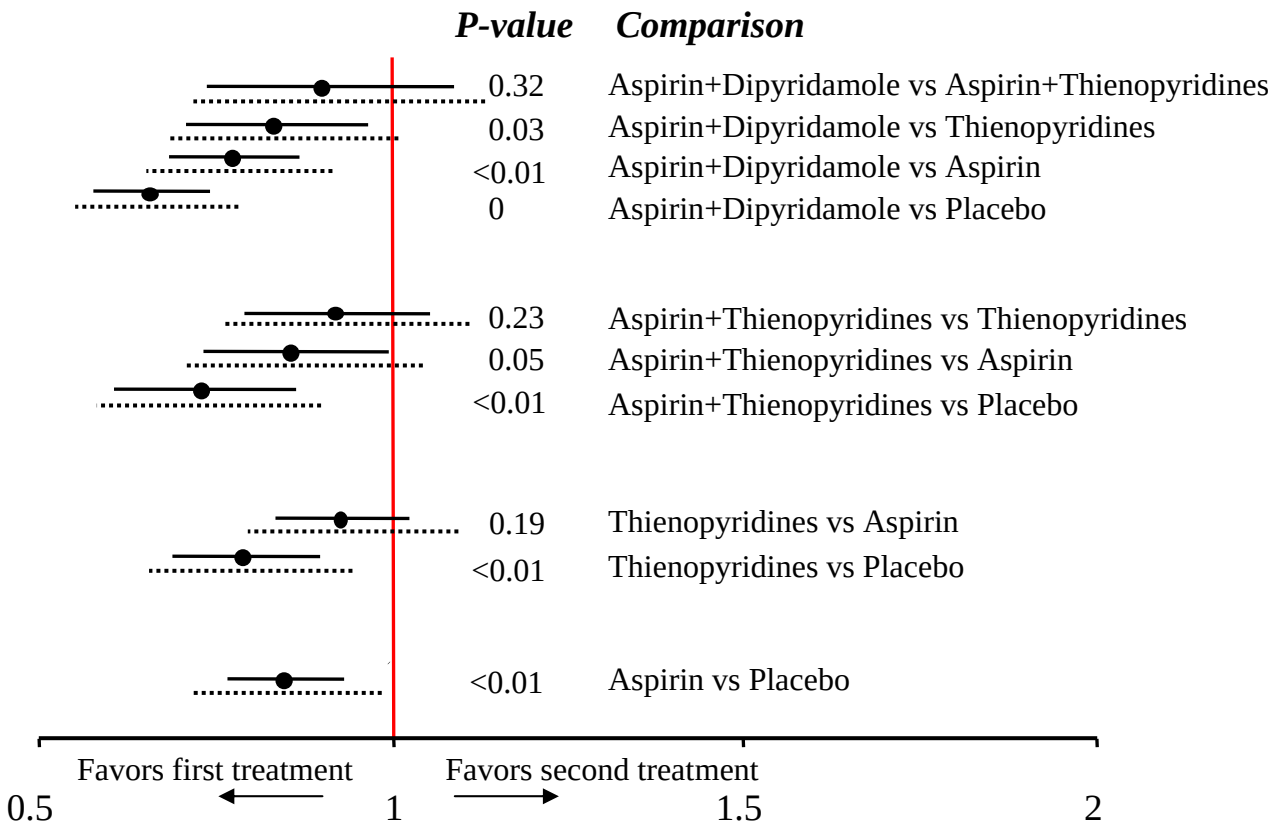
- With many treatments judgments based on pairwise effect sizes are difficult to make
- Example: Antidepressants


Efficacy (response rate) (95% CI)
Comparison
Acceptability (dropout rate) (95% CI)
BUP
1·00 (0·78–1·28)
0·75 (0·55–1·01)
1·06 (0·86–1·32)
0·89 (0·74–1·08)
0·73 (0·53–1·00)
0·87 (0·58–1·24)
0·87 (0·66–1·14)
0·81 (0·65–1·00)
0·62 (0·45–0·86)
1·01 (0·82–1·27)
0·84 (0·68–1·02)
0·98 (0·78–1·23)
CIT
0·75 (0·55–1·02)
1·07 (0·86–1·31)
0·90 (0·73–1·09)
0·73 (0·54–0·99)
0·87 (0·60–1·24)
0·87 (0·66–1·15)
0·81 (0·65–1·01)
0·62 (0·45–0·84)
1·02 (0·81–1·28)
0·84 (0·67–1·06)
1·09 (0·83–1·43)
1·12 (0·87–1·44)
DUL
1·43 (1·09–1·85)
1·19 (0·91–1·57)
0·98 (0·67–1·41)
1·16 (0·77–1·73)
1·16 (0·83–1·61)
1·08 (0·84–1·40)
0·83 (0·57–1·22)
1·36 (1·01–1·83)
1·12 (0·84–1·50)
0·82 (0·67–1·01)
0·84 (0·70–1·01)
0·75 (0·60–0·93)
ESC
0·84 (0·70–1·01)
0·69 (0·50–0·94)
0·81 (0·55–1·15)
0·81 (0·62–1·07)
0·76 (0·62–0·93)
0·58 (0·43–0·81)
0·95 (0·77–1·19)
0·78 (0·64–0·97)
1·08 (0·90–1·29)
1·10 (0·93–1·31)
0·99 (0·79–1·24)
1·32 (1·12–1·55)
FLU
0·82 (0·62–1·07)
0·97 (0·69–1·32)
0·97 (0·77–1·21)
0·91 (0·79–1·05)
0·70 (0·53–0·92)
1·14 (0·96–1·36)
0·94 (0·81–1·09)
1·10 (0·83–1·47)
1·13 (0·86–1·47)
1·01 (0·74–1·38)
1·35 (1·02–1·76)
1·02 (0·81–1·30)
FVX
1·18 (0·76–1·75)
1·18 (0·87–1·61)
1·10 (0·84–1·47)
0·85 (0·57–1·26)
1·38 (1·03–1·89)
1·14 (0·86–1·54)
1·07 (0·77–1·48)
1·09 (0·78–1·50)
0·97 (0·69–1·38)
1·30 (0·95–1·78)
0·99 (0·74–1·31)
0·97 (0·68–1·37)
MIL
0·99 (0·69–1·53)
0·94 (0·68–1·31)
0·72 (0·48–1·10)
1·17 (0·84–1·72)
0·97 (0·69–1·40)
0·79 (0·72–1·00)
0·80 (0·63–1·01)
0·72 (0·54–0·94)
0·96 (0·76–1·19)
0·73 (0·60–0·88)
0·71 (0·55–0·92)
0·74 (0·53–1·01)
MIR
0·93 (0·75–1·17)
0·72 (0·51–1·03)
1·17 (0·91–1·51)
0·97 (0·76–1·23)
1·06 (0·87–1·30)
1·08 (0·90–1·30)
0·97 (0·78–1·20)
1·30 (1·10–1·53)
0·98 (0·86–1·12)
0·96 (0·76–1·23)
1·00 (0·74–1·33)
1·35 (1·11–1·64)
PAR
0·77 (0·56–1·05)
1·25 (1·04–1·52)
1·03 (0·86–1·24)
1·60 (1·20–2·16)
1·63 (1·25–2·14)
1·46 (1·05–2·02)
1·95 (1·47–2·59)
1·48 (1·16–1·90)
1·45 (1·03–2·02)
1·50 (1·03–2·18)
2·03 (1·52–2·78)
1·50 (1·16–1·98)
REB
1·63 (1·19–2·24)
1·34 (0·99–1·83)
0·87 (0·72–1·05)
0·88 (0·72–1·07)
0·79 (0·62–1·01)
1·06 (0·88–1·27)
0·80 (0·69–0·93)
0·79 (0·61–1·01)
0·81 (0·60–1·11)
1·10 (0·90–1·36)
0·82 (0·69–0·96)
0·54 (0·41–0·71)
SER
0·82 (0·67–1·00)
0·85 (0·70–1·01)
0·86 (0·71–1·05)
0·77 (0·60–0·99)
1·03 (0·86–1·24)
0·78 (0·68–0·90)
0·77 (0·59–0·99)
0·79 (0·58–1·08)
1·08 (0·87–1·33)
0·79 (0·67–0·94)
0·53 (0·40–0·69)
0·98 (0·82–1·16)
VEN

Ranking measures from MTM

- With many treatments judgments based on pairwise effect sizes are difficult to make
- Example: Antidepressants
- Example: Antiplatelet regimens for serious vascular events

Serious vascular events with antiplatelet regimens



Odds Ratio for serious vascular event

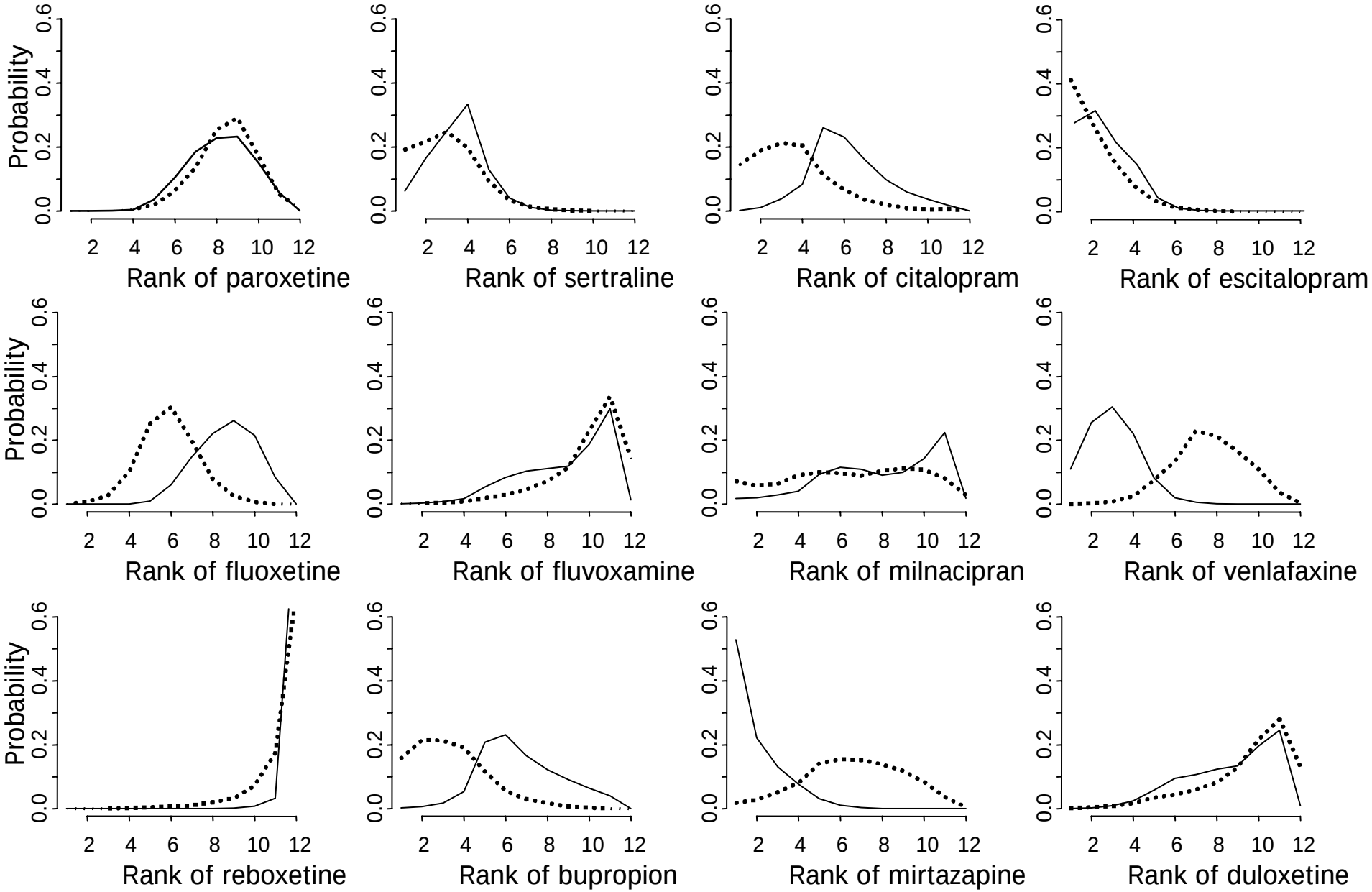
Probabilities instead of effect sizes

- Estimate for each treatment ***the probability to be the best***
- This is straightforward within a Bayesian framework

% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00

% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00
j=2	0.25	0.25	0.50	0.00
j=3	0.25	0.25	0.25	0.25
j=4	0.25	0	0	0.75

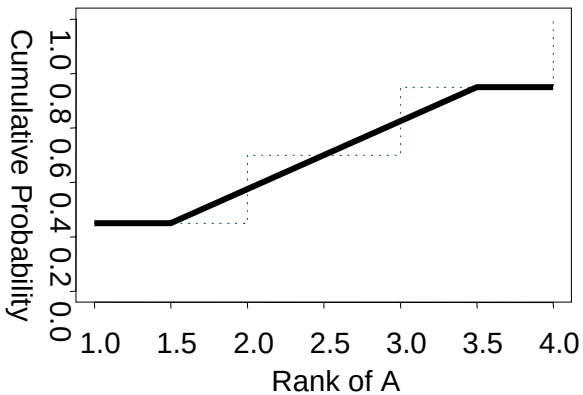
i the treatment
j the rank

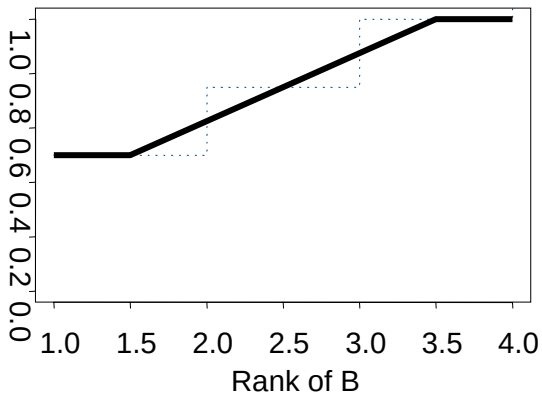


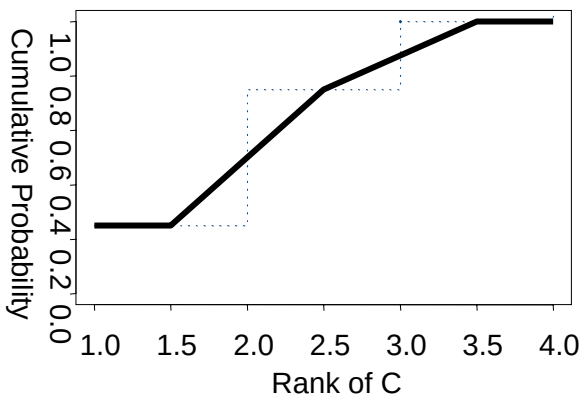
Ranking for efficacy (solid line) and acceptability (dotted line). Ranking: probability to be the best treatment, to be the second best, the third best and so on, among the 12 comparisons).

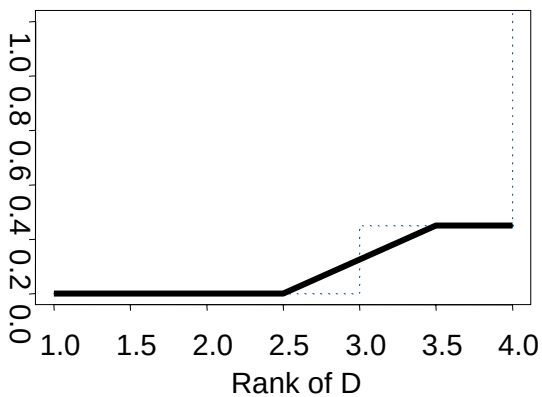
% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00
j=2	0.50	0.75	0.75	0.00
j=3	0.75	1.00	1.00	0.25
j=4	1.00	1.00	1.00	1.00

i the treatment
j the rank





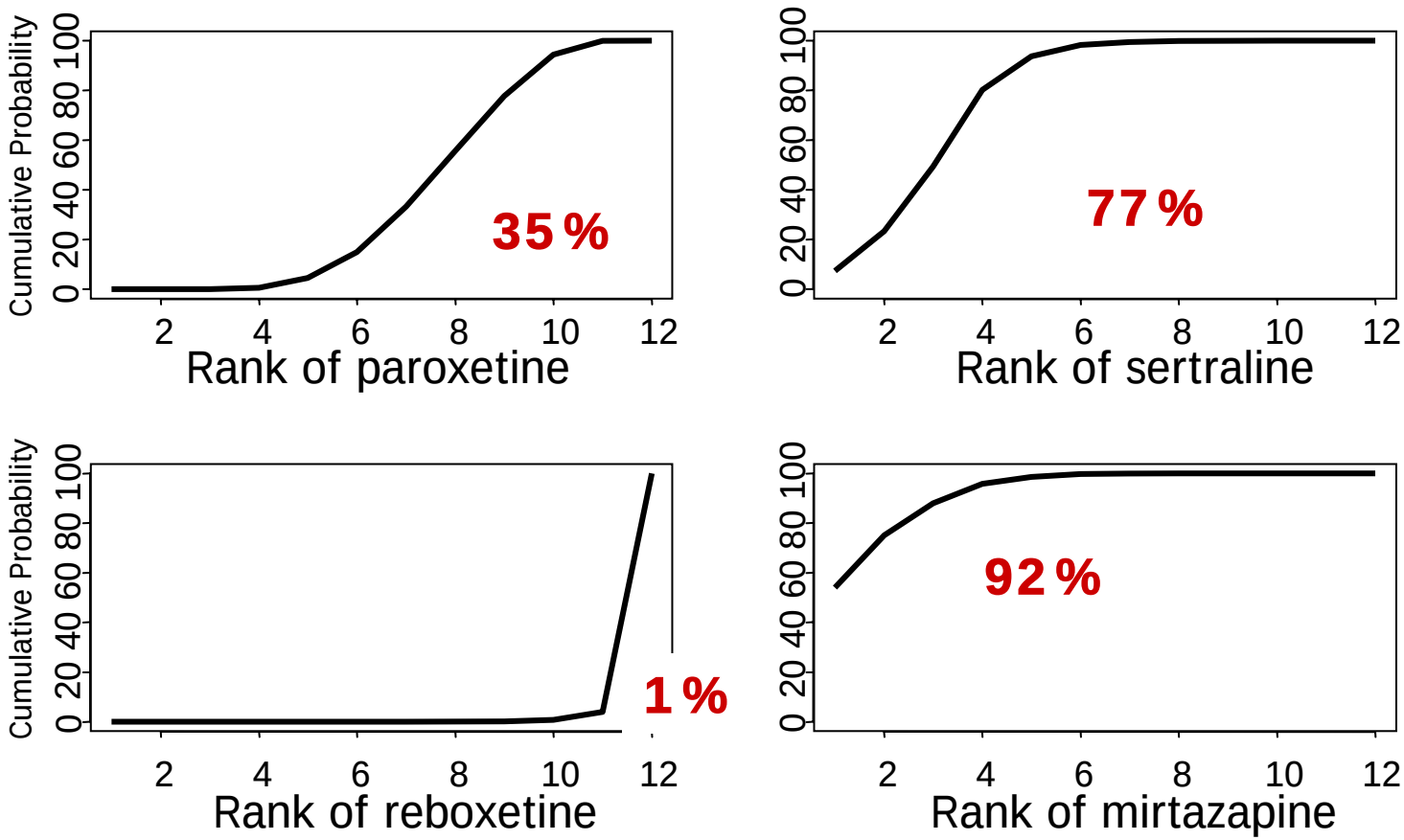




The areas under the cumulative curves for the four treatments of the example above are
A=0.5
B=0.75
C=0.67
D=0.08

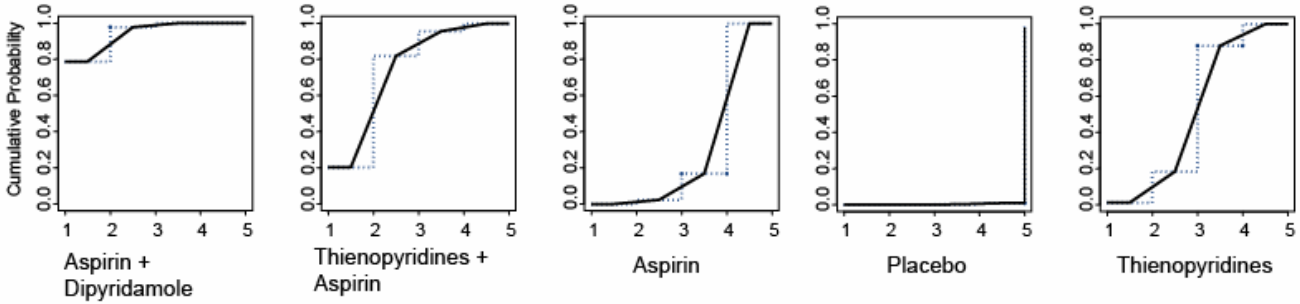
1. A comprehensive ranking measure

Preliminary results for ranking 12 antidepressants

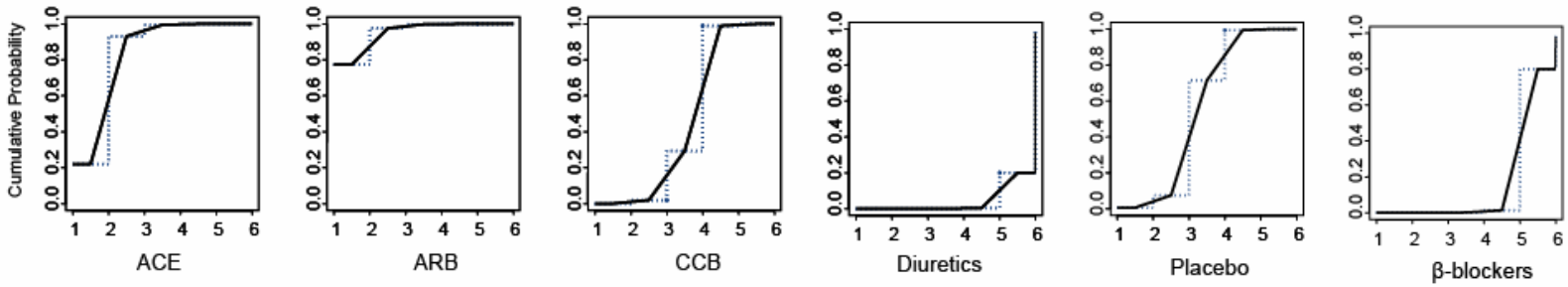


Compared to an imaginary antidepressant which is ‘always the best’, mirtazapine reaches up to 92% of its potential!

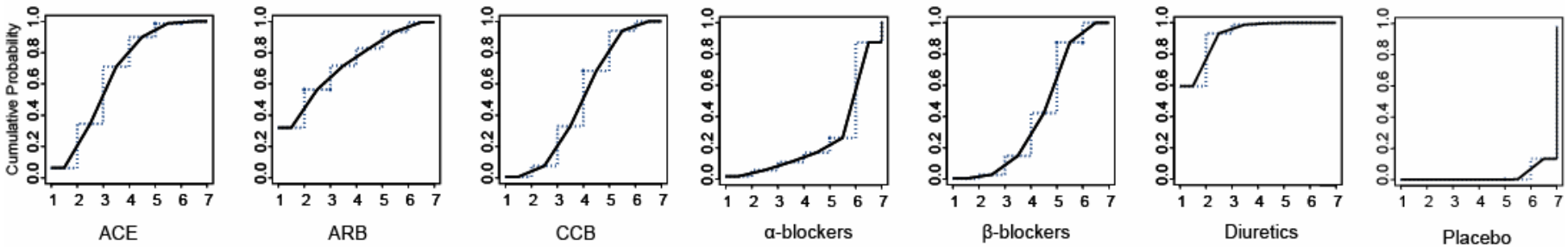
Serious vascular events with antiplatelet regimens

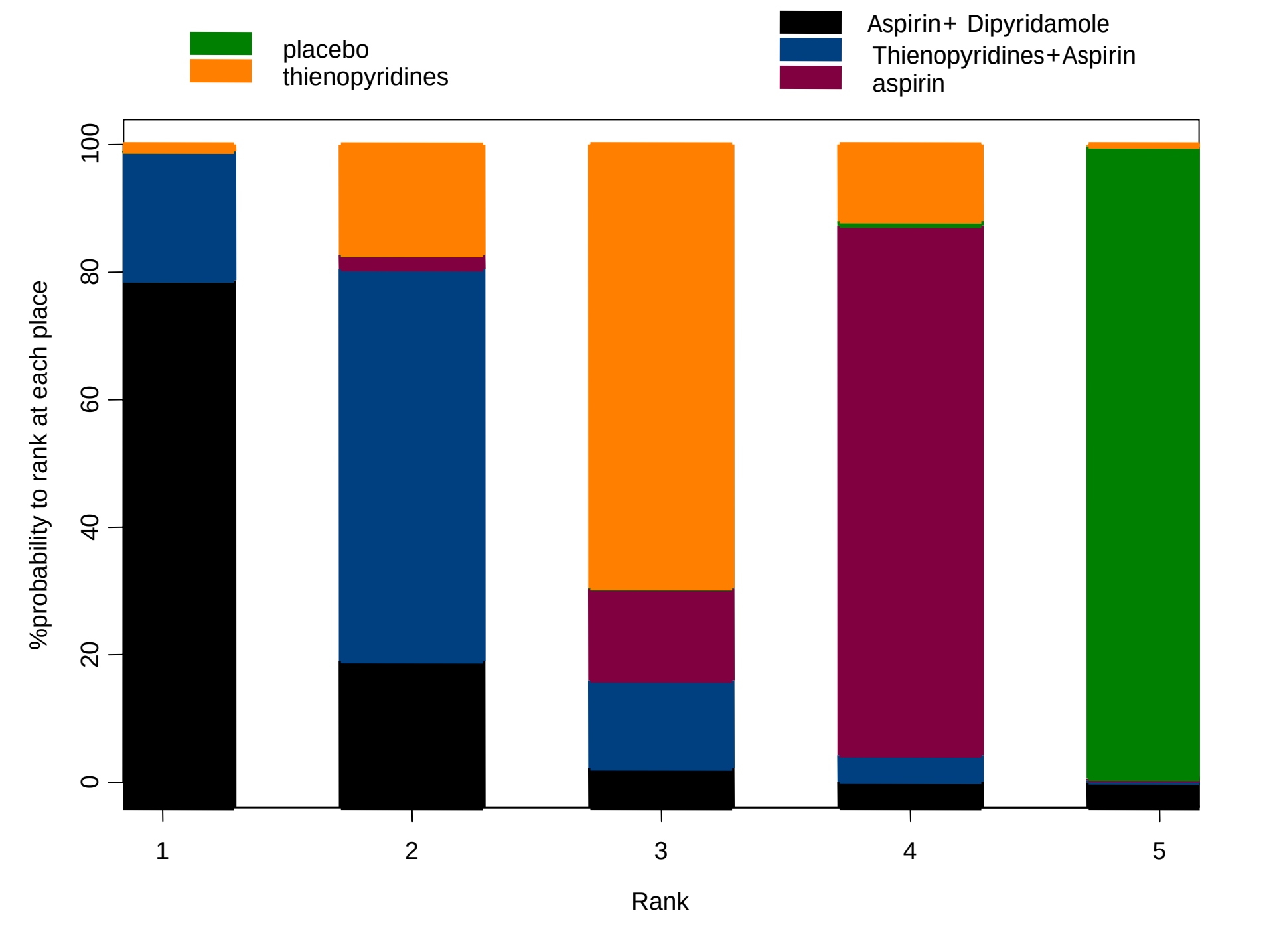


Incident diabetes with antihypertensive drugs



Serious cardiovascular event with antihypertensive drugs




placebo
thienopyridines
Aspirin+ Dipyridamole
Thienopyridines+Aspirin
aspirin
%probability to rank at each place
0
20
40
60
80
100
1
2
3
4
5
Rank

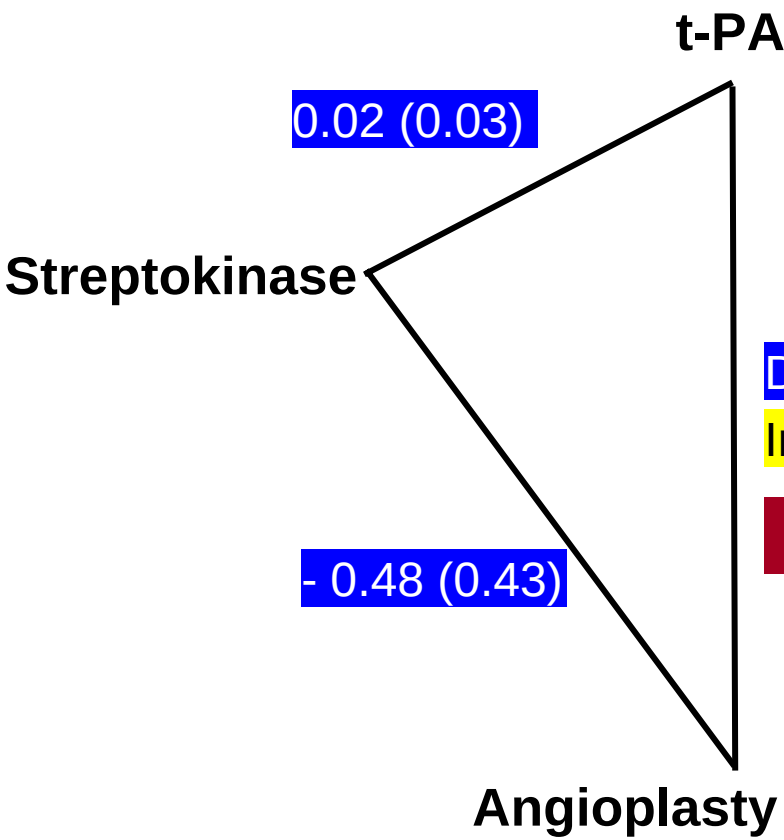
Inconsistency

- What is inconsistency?
- How it manifests itself?

Inconsistency

LOR (SE) for MI

Calculate a difference between direct and indirect estimates



Direct t-PA vs Angioplasty= – 0.41 (0.36)

Indirect t-PA vs Angioplasty = – 0.46 (0.18)

Inconsistency Factor IF = 0.05

Inconsistency - Heterogeneity

- *Heterogeneity:* ‘excessive’ discrepancy among study-specific effects
- *Inconsistency:* it is the excessive discrepancy among source-specific effects (direct and indirect)

Inconsistency

Empirical Evidence

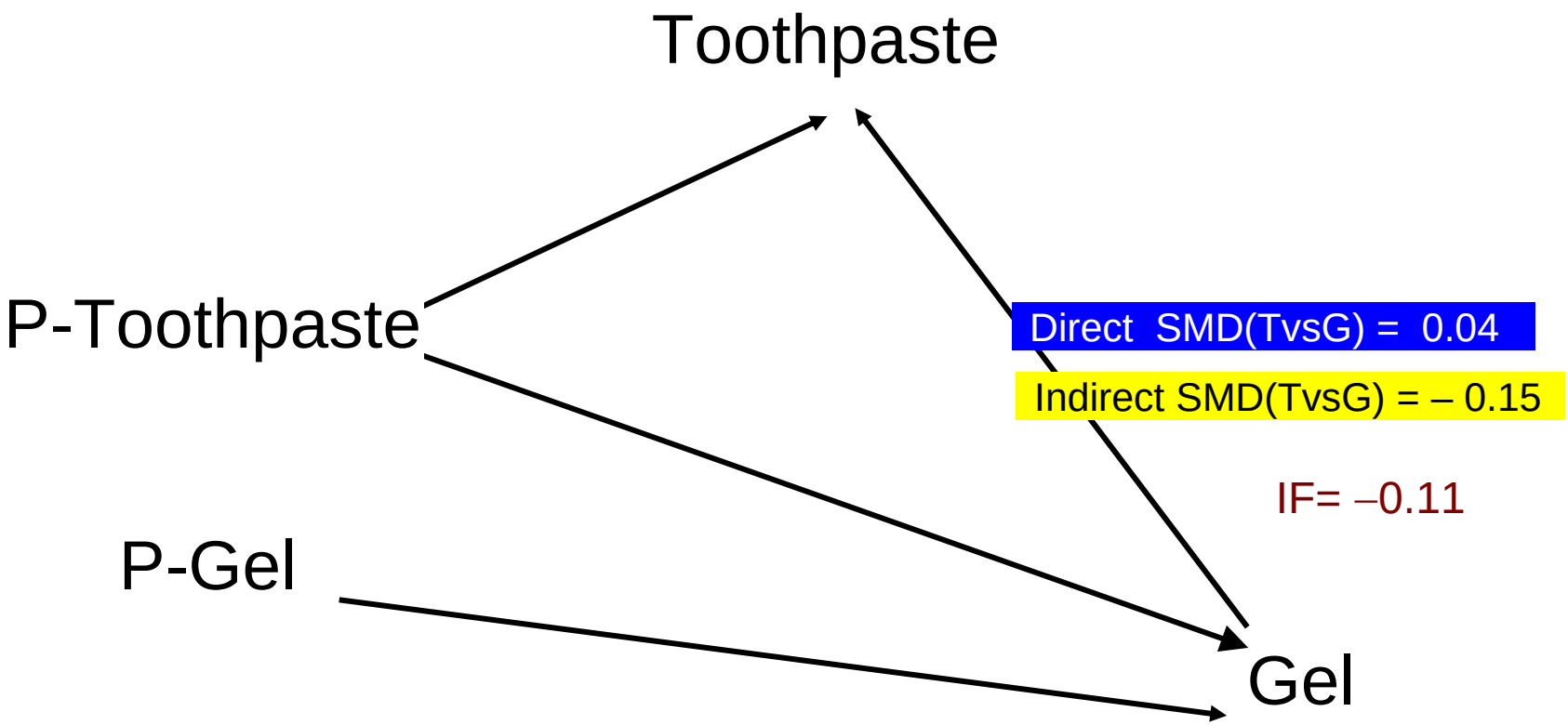
- In 3 cases out of 44 there was an important discrepancy between direct/indirect effect.
- Direction of the discrepancy is inconsistent

Glenny et al HTA 2005

What can cause inconsistency?

Inappropriate common comparator

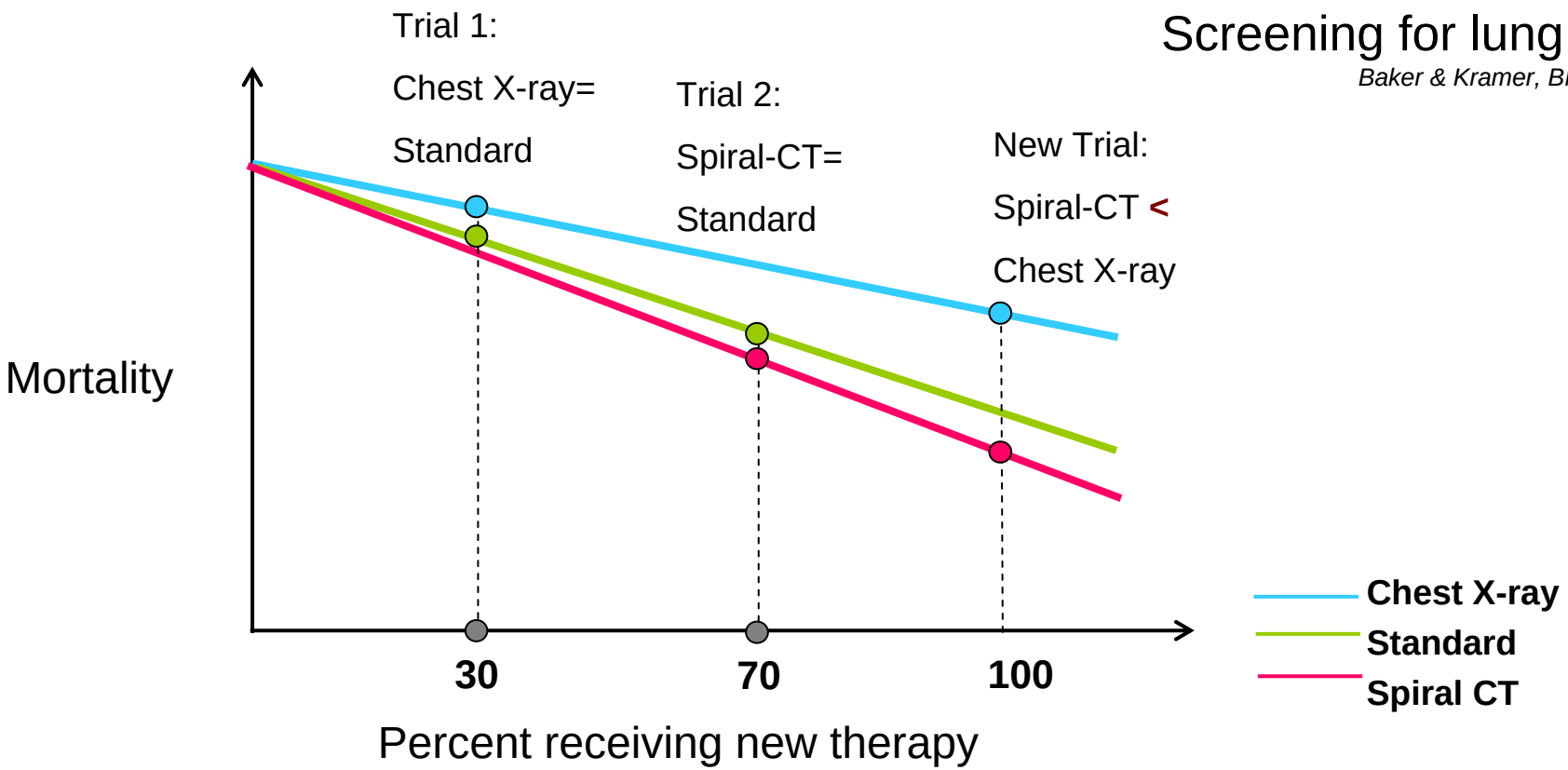
Compare Fluoride treatments in preventing dental caries



I cannot learn about Toothpaste versus Gel through Placebo!

What can cause inconsistency?

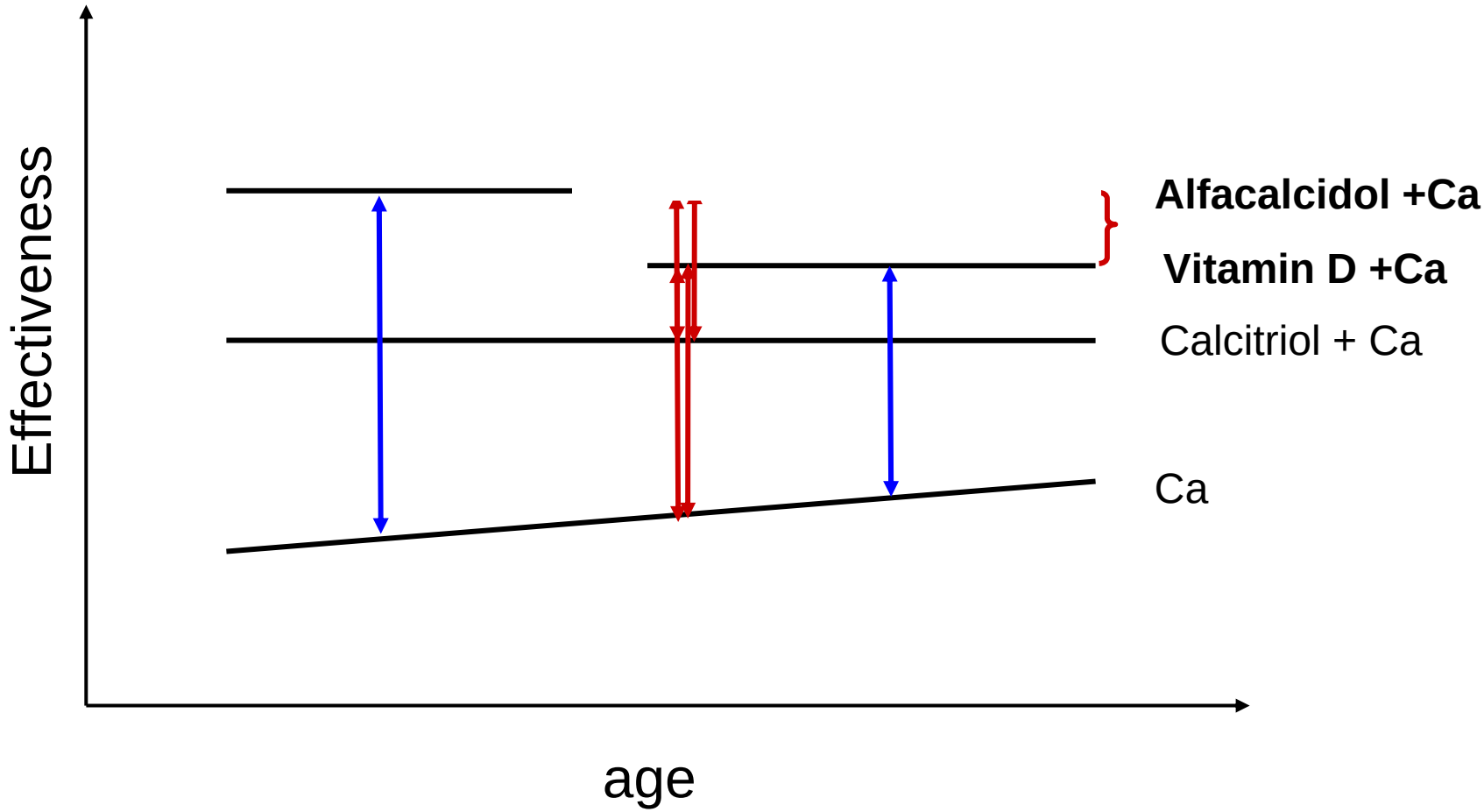
Confounding by trial characteristics



A new therapy (possibly unreported in the trials) decreases the mortality but in different rates for the three screening methods

What can cause inconsistency?

Confounding by trial characteristics



Different characteristics across comparisons may cause inconsistency

Assumptions of MTM

- There is **not confounding** by trial characteristics that are related to both the comparison being made and the magnitude of treatment difference
- The trials in two different comparisons are **exchangeable** (other than interventions being compared)
- Equivalent to the assumption ***'the unobserved treatment is missing at random'***
  - *Is this plausible?*
  - *Selection of the comparator is not often random!*

Inconsistency

Detecting

- Check the distribution of important characteristics per treatment comparison
  - Usually unobserved….
  - Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM

Compare the characteristics!

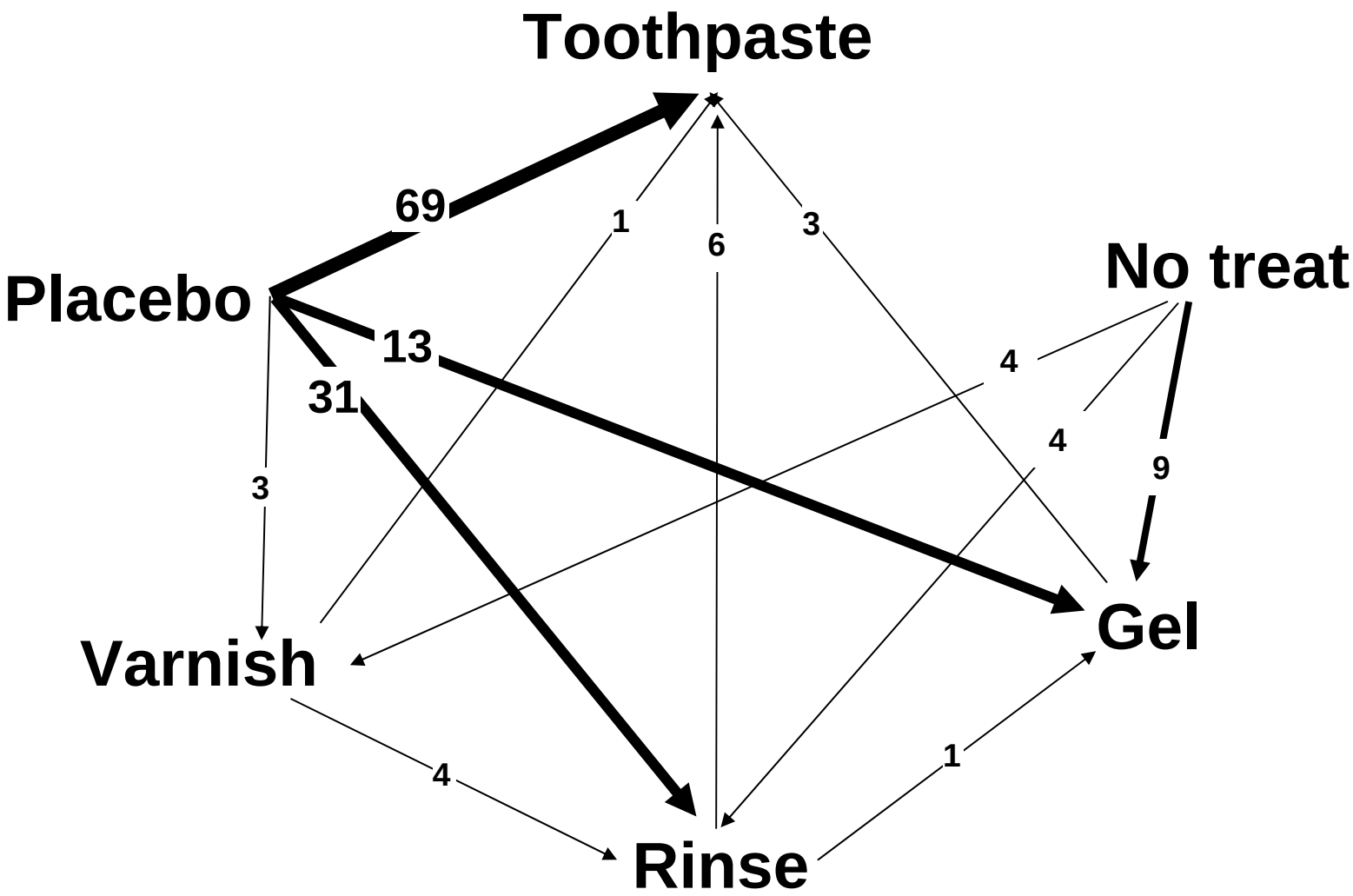
No. studies	T	G	R	V	P	Fup	Baseline	Year	Water F (yes/no)
69	■				■	2.6	11.8	1968	0.2
13		■			■	2.3	3.8	1973	0.2
30			■		■	2.4	5.9	1973	0.1
3				■	■	2.3	2.7	1983	0
3	■	■				2.7	NA	1968	0.66
6	■		■			2.8	14.7	1969	0
1	■			■		2	0.9	1978	0
1		■	■			1	NA	1977	0
1		■		■		3	7.4	1991	NA
4			■	■		2.5	7.6	1981	0.33

Salanti G, Marinho V, Higgins JP: **A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered.** *J Clin Epidemiol* 2009, **62:** 857-864.

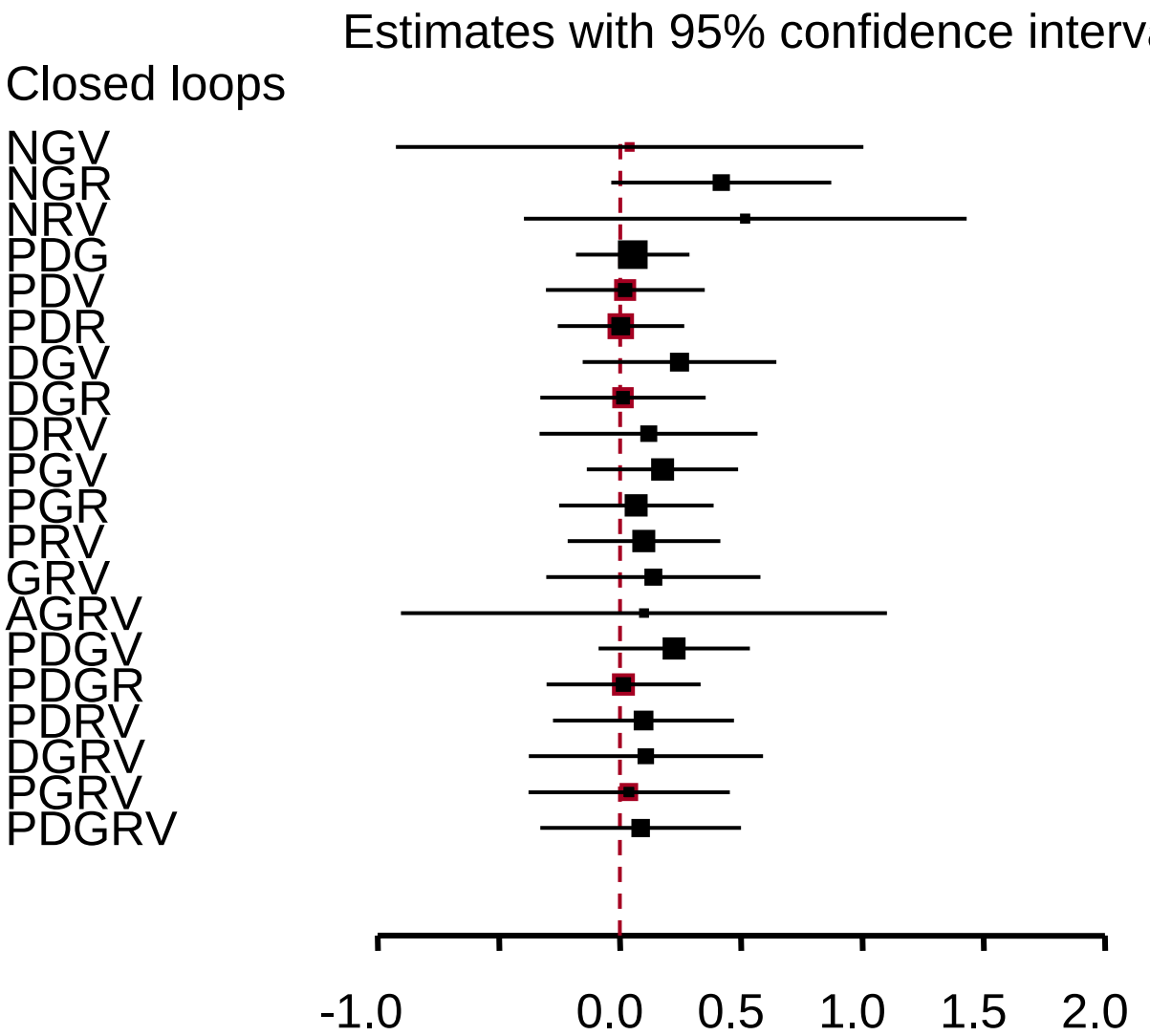
Inconsistency

Detecting

- Check the distribution of important characteristics per treatment comparison
  - Usually unobserved….
  - Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM
- Get a taste by looking for inconsistency in closed loops


Toothpaste
69
1
6
3
No treat
Placebo
13
4
31
4
9
3
Gel
Varnish
4
1
Rinse

Evaluation of concordance within closed loops



R routine in http://www.dhe.med.uoi.gr/software.htm

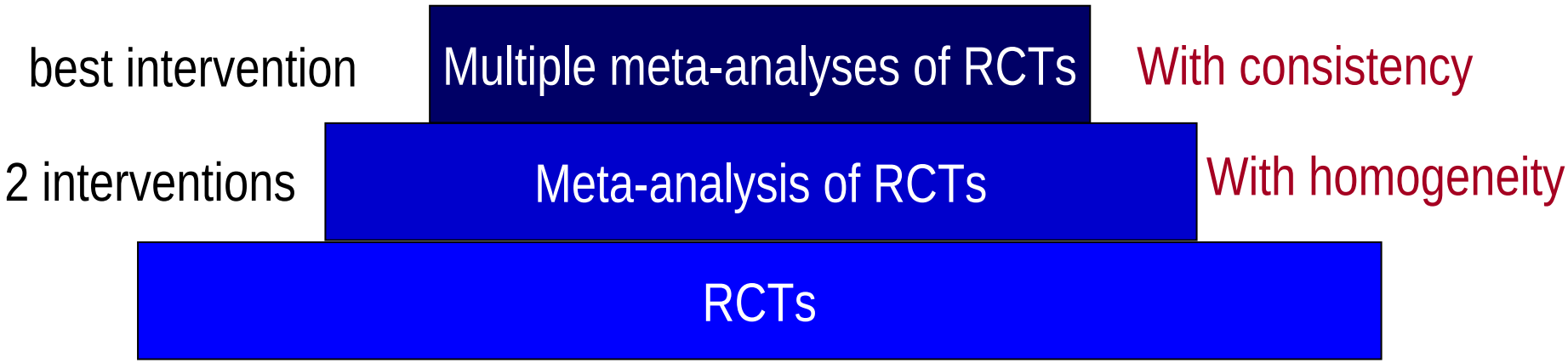
Salanti G, Marinho V, Higgins JP: **A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered.** *J Clin Epidemiol* 2009, **62:** 857-864.

Inconsistency

Detecting

- Check the distribution of important characteristics per treatment comparison
  - Usually unobserved….
  - Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM
- Get a taste by looking for inconsistency in closed loops
- Fit a model that relaxes consistency
  - Add an extra *'random effect' per loop (Lu & Ades JASA 2005*)

Inconsistency - Heterogeneity



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