THE CAMPBELL COLLABORATION

What helps? What harms? Based on what evidence?

Network Meta- Analysis

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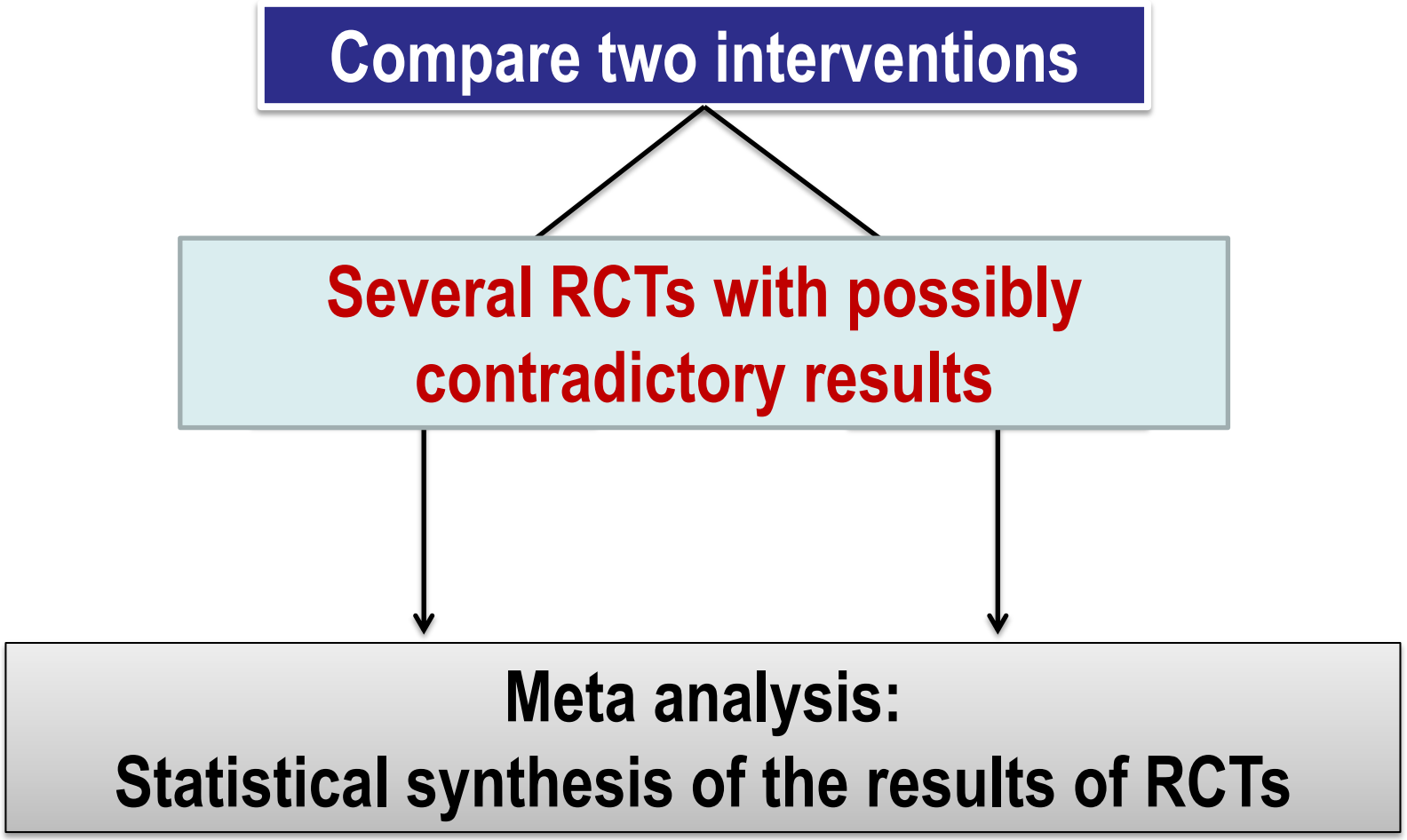
Standard meta-analysis

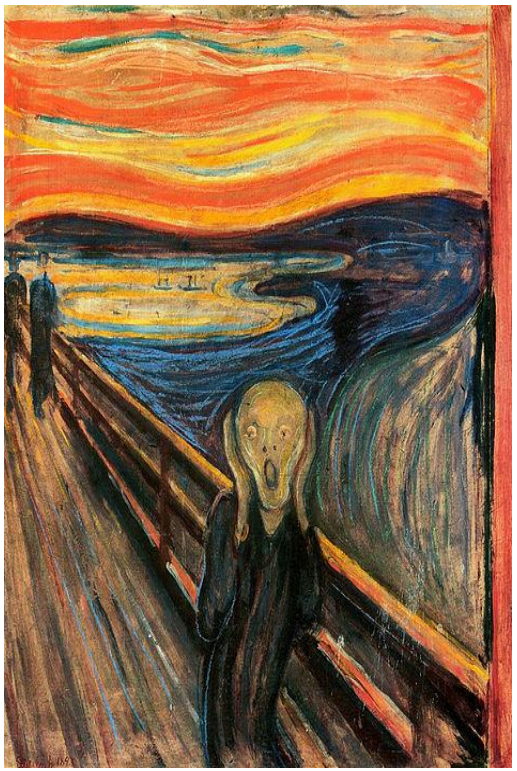


Anxiety disorder in children and adolescents

- Ipser JC, SteinDJ, Hawkridge S, Hoppe L. **Pharmacotherapy** for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews 2009, Issue 3. [DOI:10.1002/14651858.CD005170.pub2]

- James AC, James G, Cowdrey FA, Soler A, Choke A. **Cognitive behavioural therapy** for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD004690. DOI: 10.1002/14651858.CD004690.pub3.

- Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F. **Exercise** n prevention and treatment of anxiety and depression among children and young people. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004691. DOI: 10.1002/14651858.CD004691.pub2.



12 new generation antidepressants

sertraline

milnacipran

reboxetine

paroxetine

mirtazapine

duloxetine

fluvoxamine

escitalopram

citalopram

bupropion

venlafaxine

fluoxetine

12 new generation antidepressants

several meta-analyses have been published

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

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

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

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

12 new generation antidepressants

several meta-analyses have been published

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

Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

Andrea Cipriani, Toshiaki A Furukawa, Georgia Salanti, John R Geddes, Julian P T Higgins, Rachel Churchill, Norio Watanabe, Atsuo Nakagawa, Ichiro M Omori, Hugh McGuire, Michele Tansella, Corrado Barbui

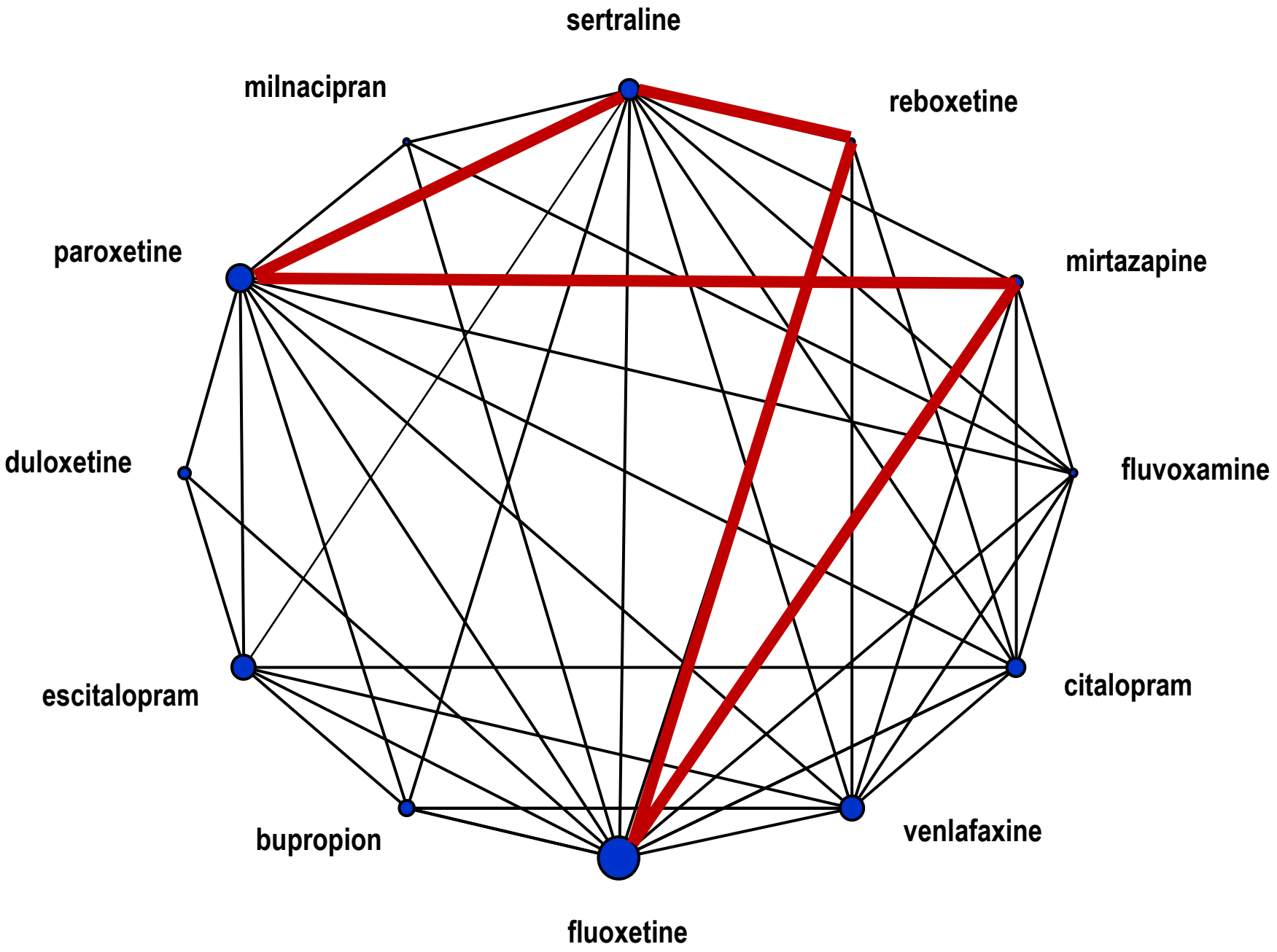
Summary

Background Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression.

Methods We systematically reviewed 117 randomised controlled trials (25 928 participants) from 1991 up to Nov 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis.

Findings Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1·39, 1·33, 1·30 and 1·27, respectively), fluoxetine (1·37, 1·32, 1·28, and 1·25, respectively), fluvoxamine (1·41, 1·35, 1·30, and 1·27, respectively), paroxetine (1·35, 1·30, 1·27, and 1·22, respectively), and reboxetine (2·03, 1·95, 1·89, and 1·85, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.

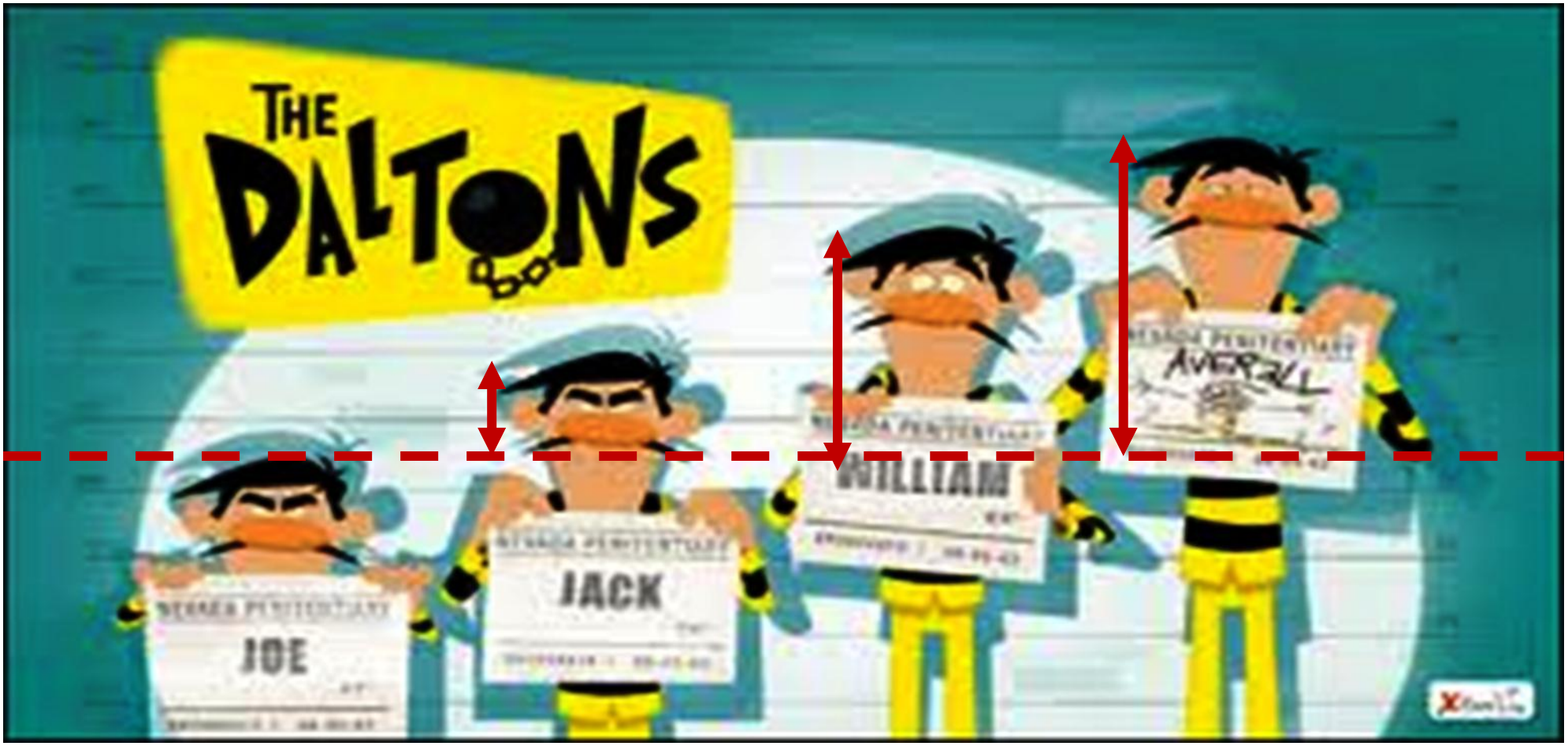
Interpretation Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.



Cipriani, Fukurawa, Salanti et al. Lancet 2009

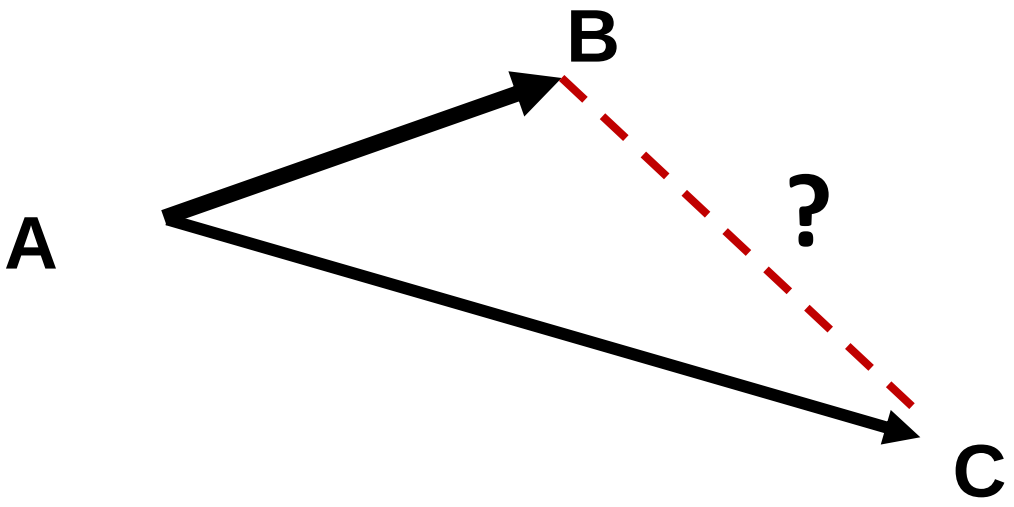
Indirect comparison

- If we know how much taller is Averail to Joe and how much taller is Jack to Joe, we know how much taller is Averail to Jack



Indirect comparison

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

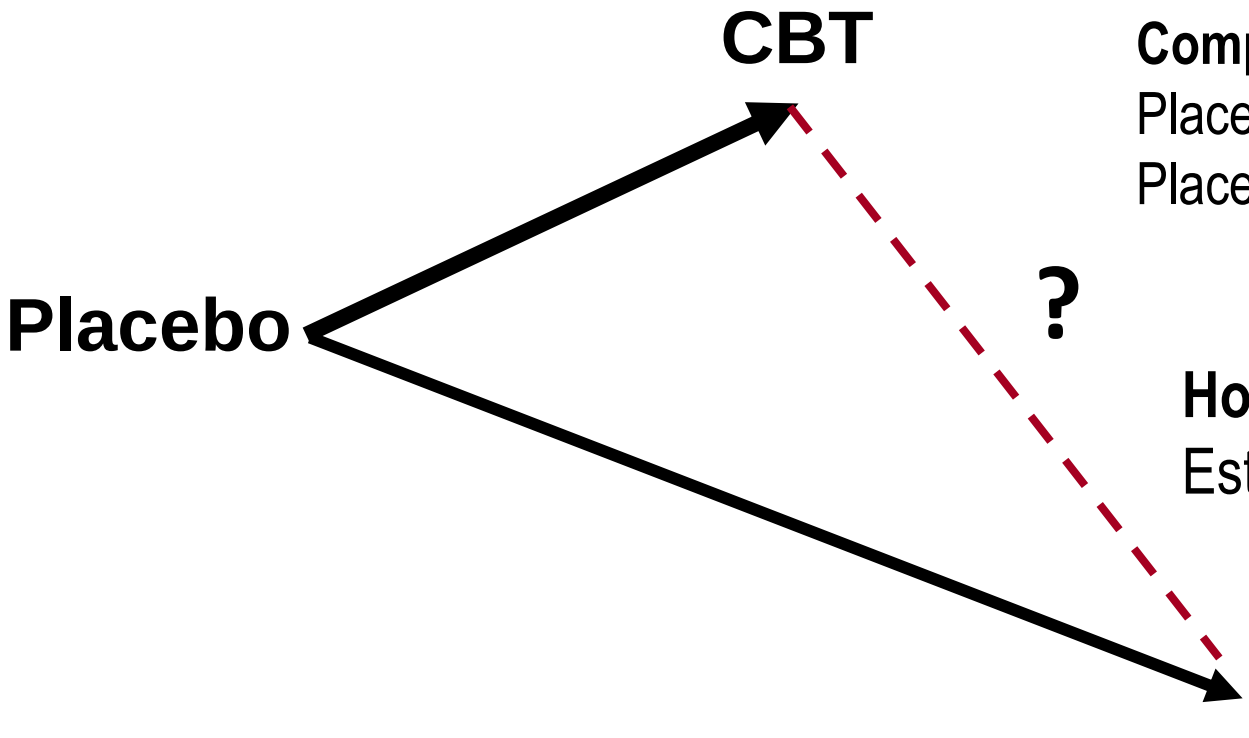


$$\mu_{BC}^{ind} = \mu_{AC}^{dir} - \mu_{AB}^{dir}$$

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

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

Example: CBT vs SSRI



Comparison	SMD	CI	S.E.
Placebo vs CBT	-0.34	(-0.41, -0.28)	0.03
Placebo vs SSRI	-0.19	(-0.30, -0.10)	0.05

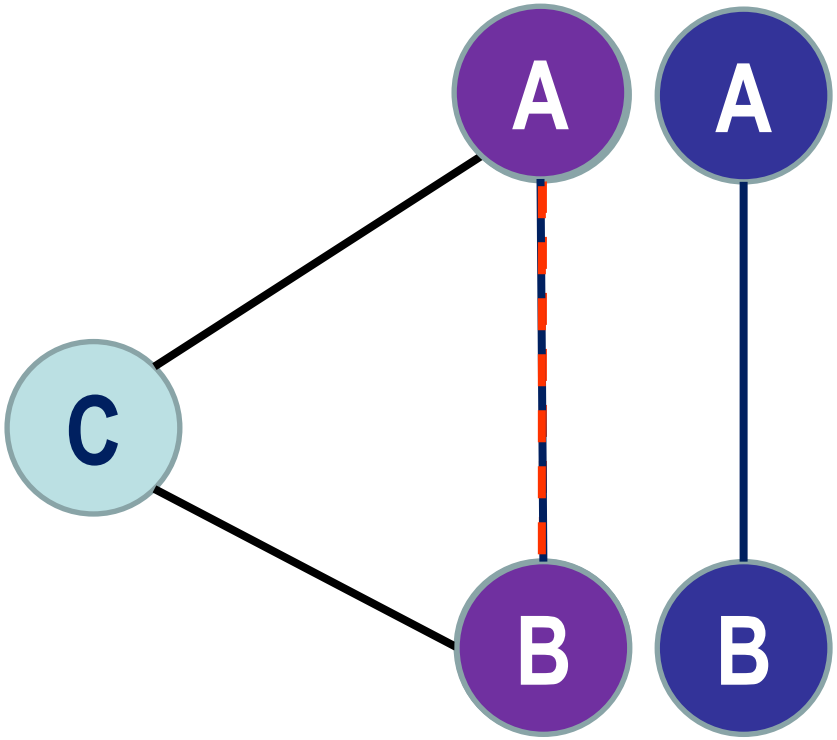
How to compare SSRI to CBT ?

Estimate indirect SMD and a 95% CI

$$\mu^{ind}_{SSRIvsCBT} = -0.34 - (-0.19) = -0.15 \quad v^{ind}_{SSRIvsCBT} = 0.03^2 + 0.05^2 = 0.0034$$

$$\mu^{ind}_{SSRIvsCBT} \pm 1.96\sqrt{v^{ind}_{SSRIvsCBT}} = -0.15 \pm 1.96\sqrt{0.0034} = (-0.26, -0.04)$$

Indirect and mixed/NMA effects



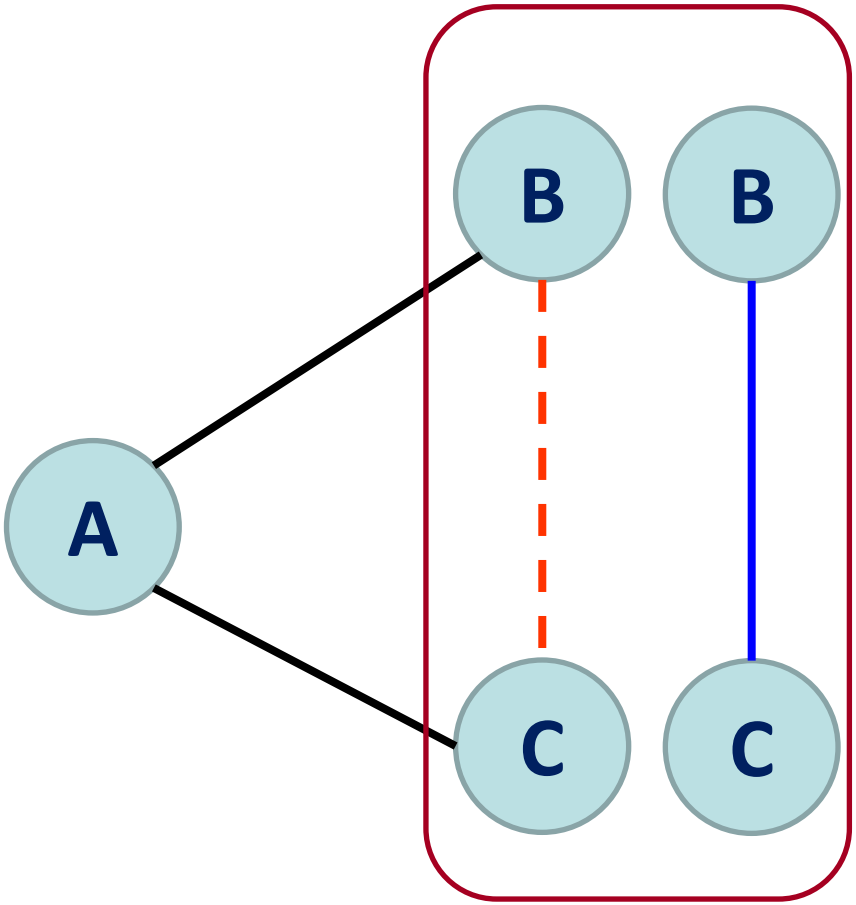
Indirect effect

Direct effect

NMA effect

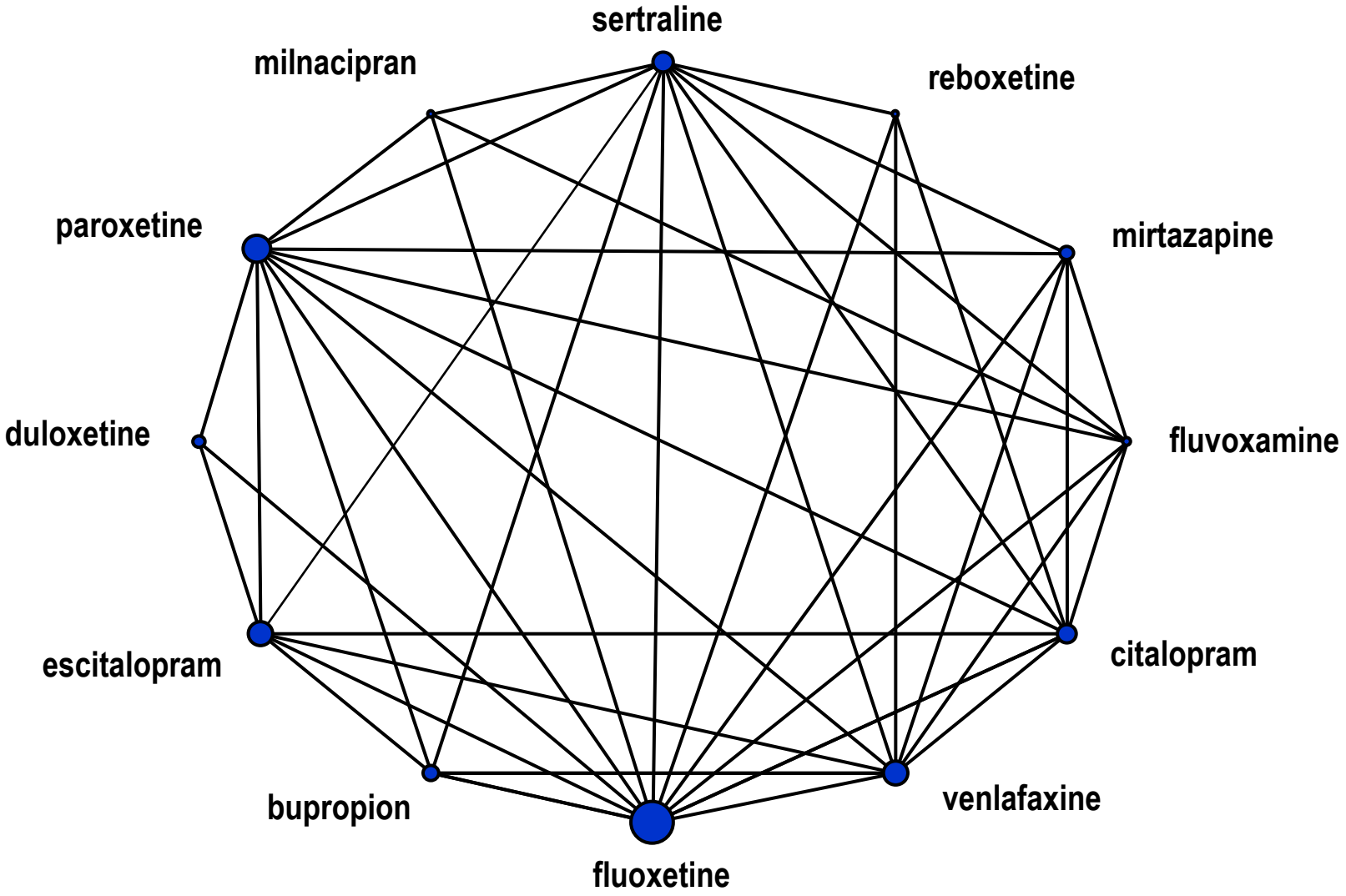
Consistency

Direct and indirect evidence are in agreement



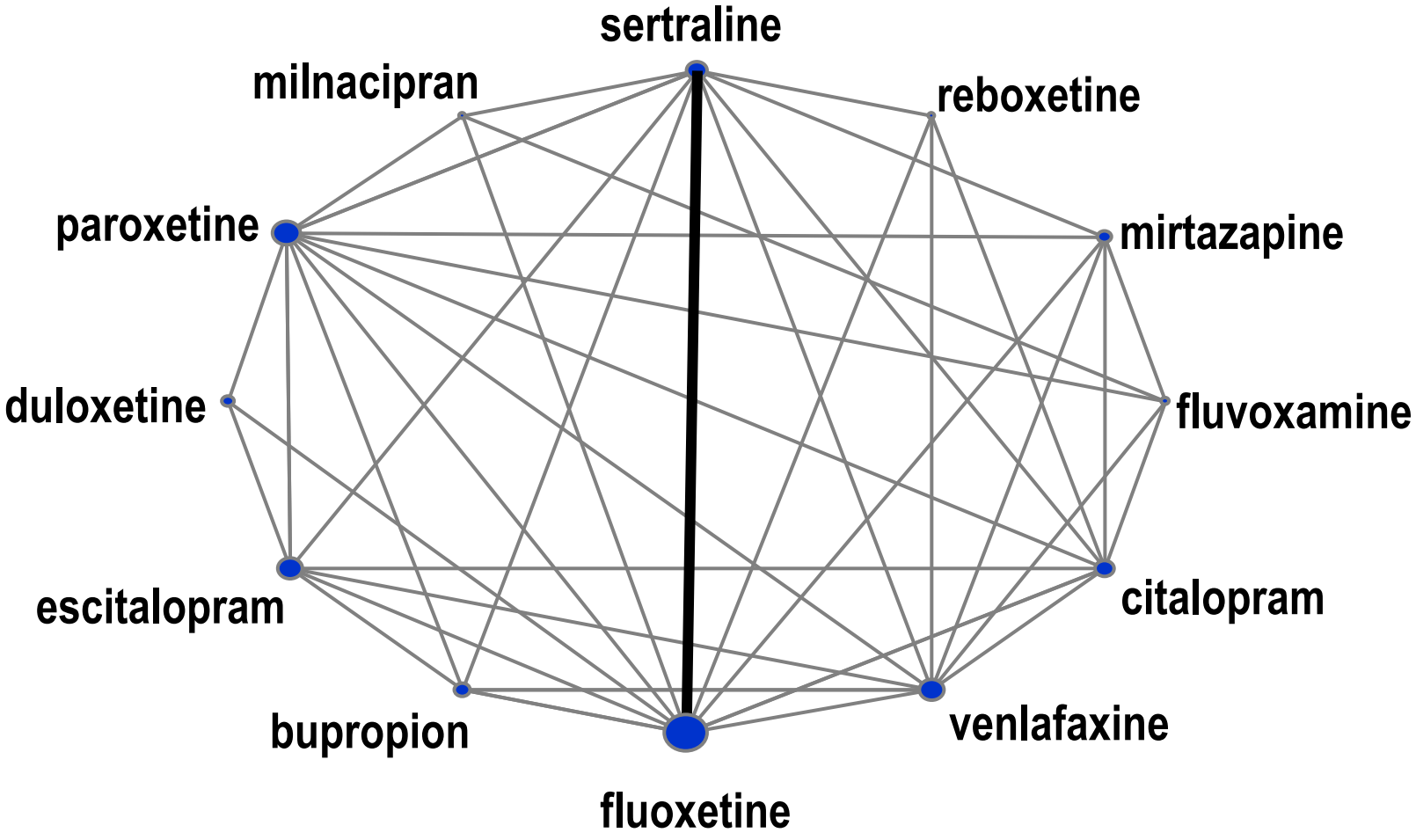
$$\mu^{ind} = \mu^{dir}$$

Network plot of 12 antidepressants



Cipriani, Fukurawa, Salanti et al. Lancet 2009

Network of experimental comparisons



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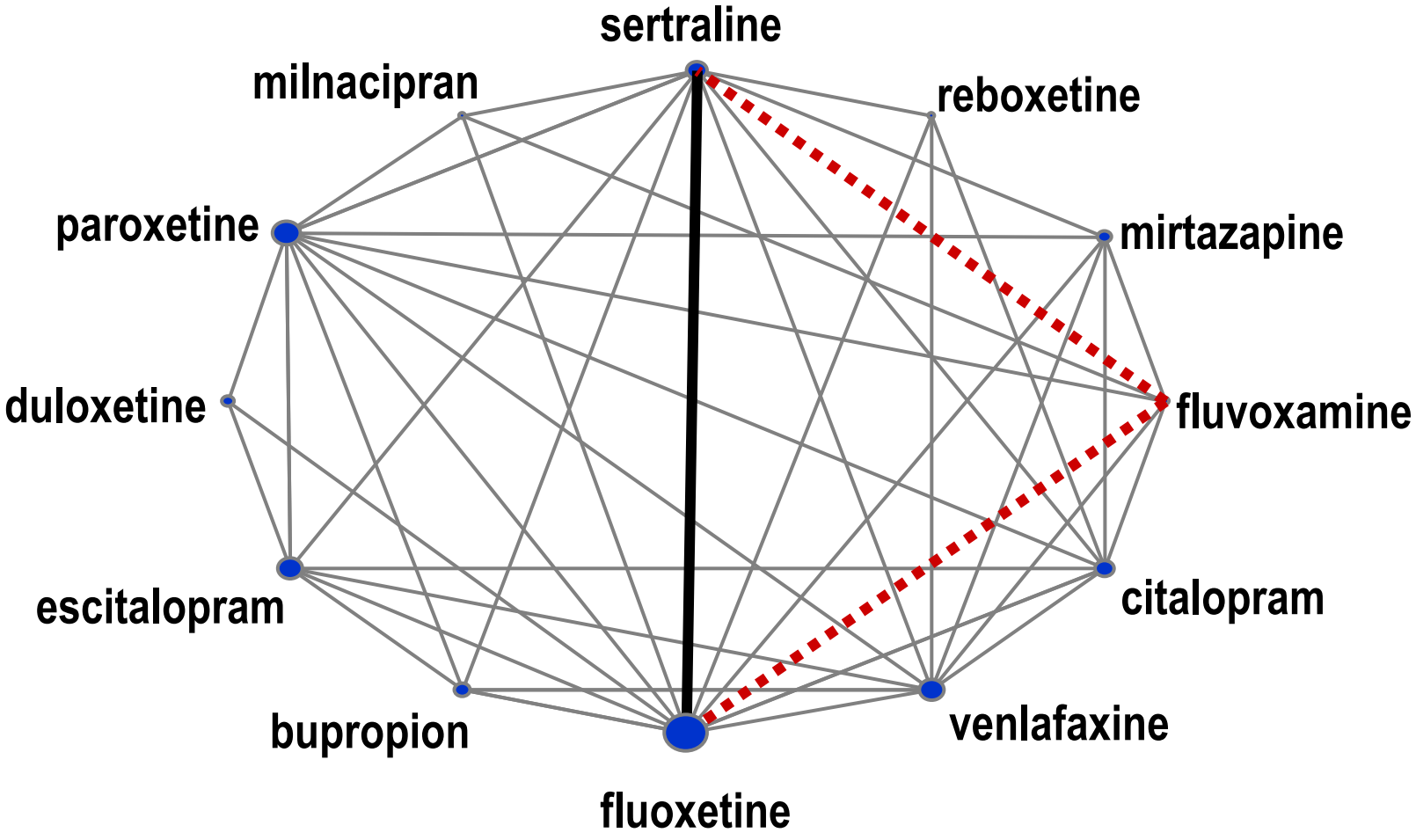

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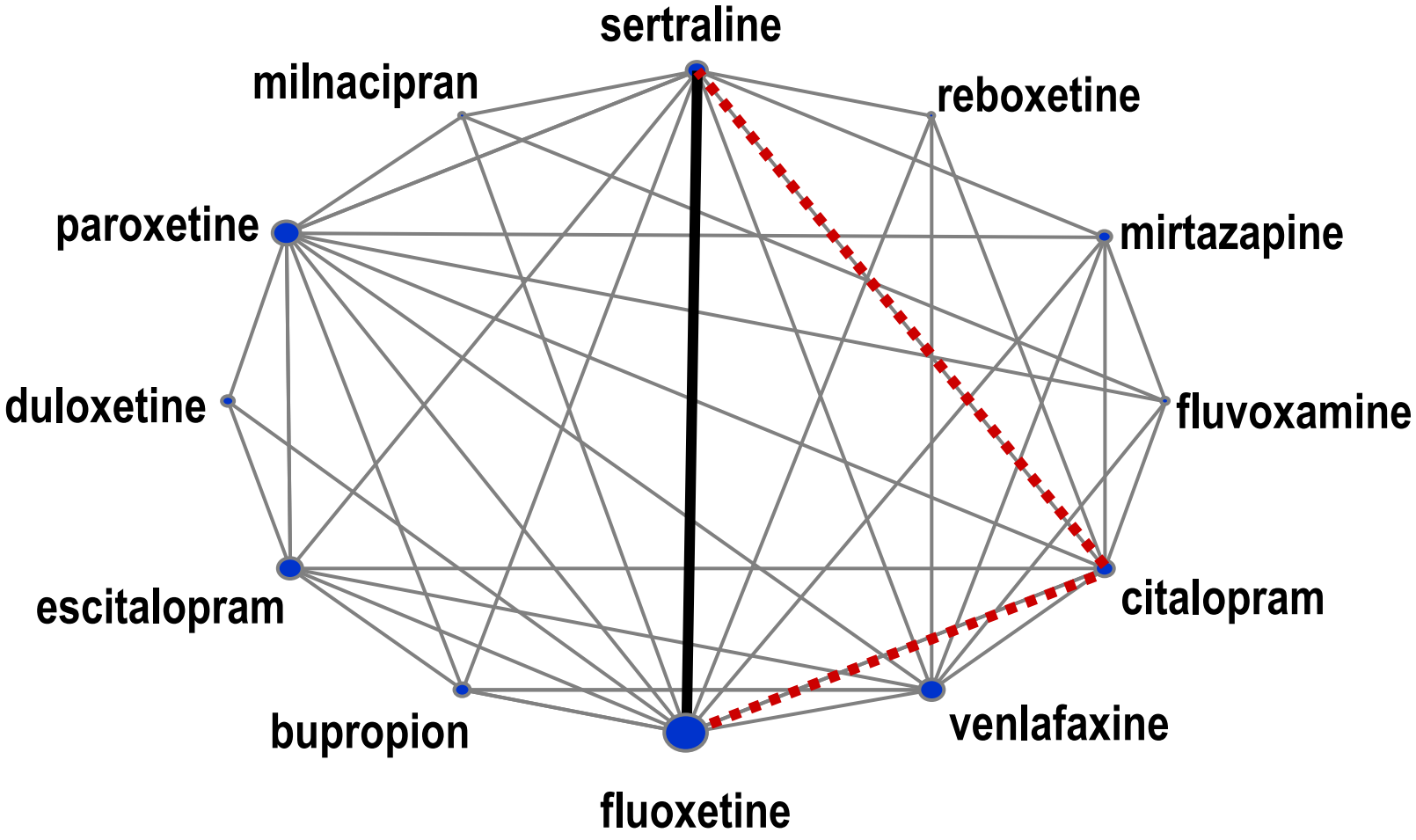
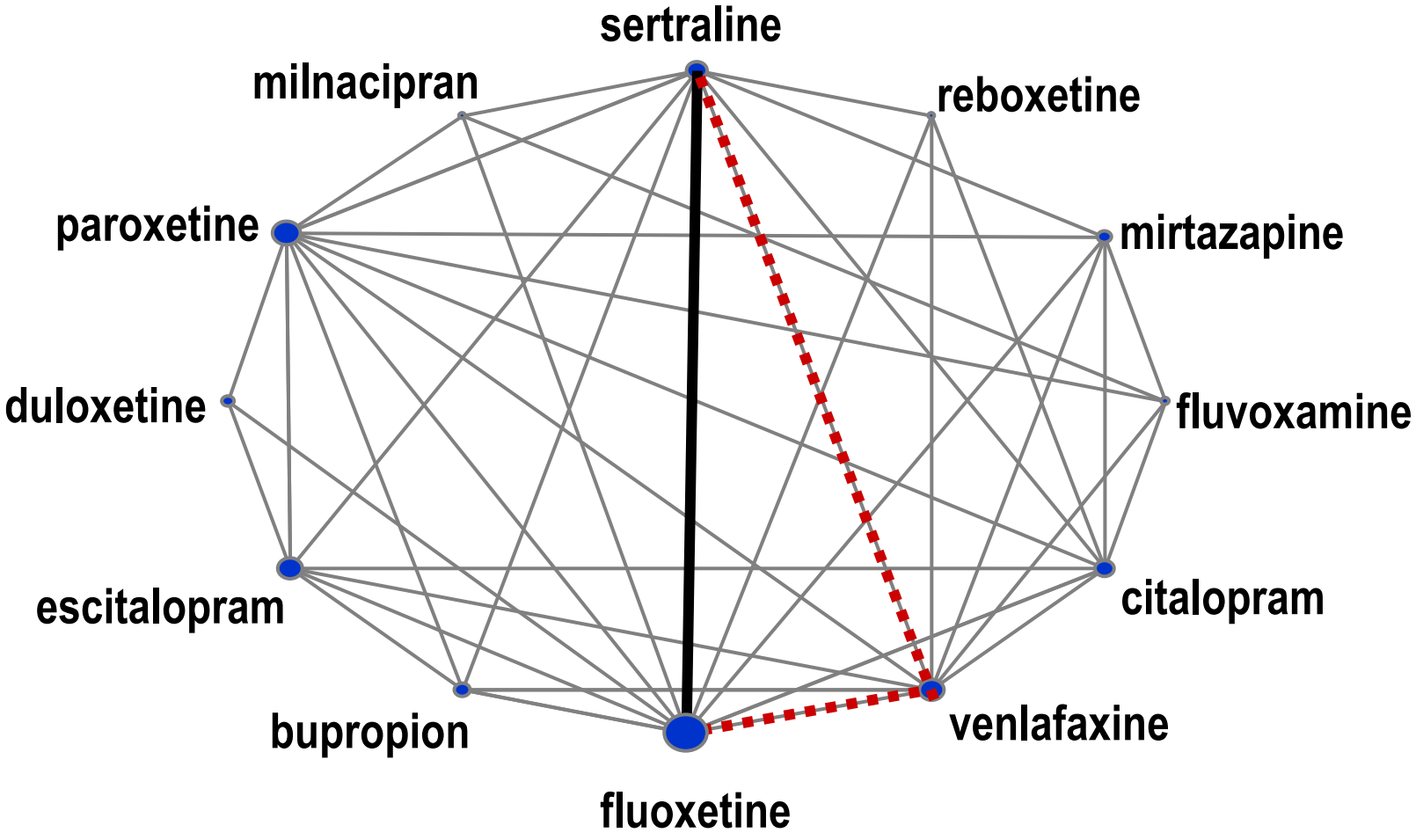
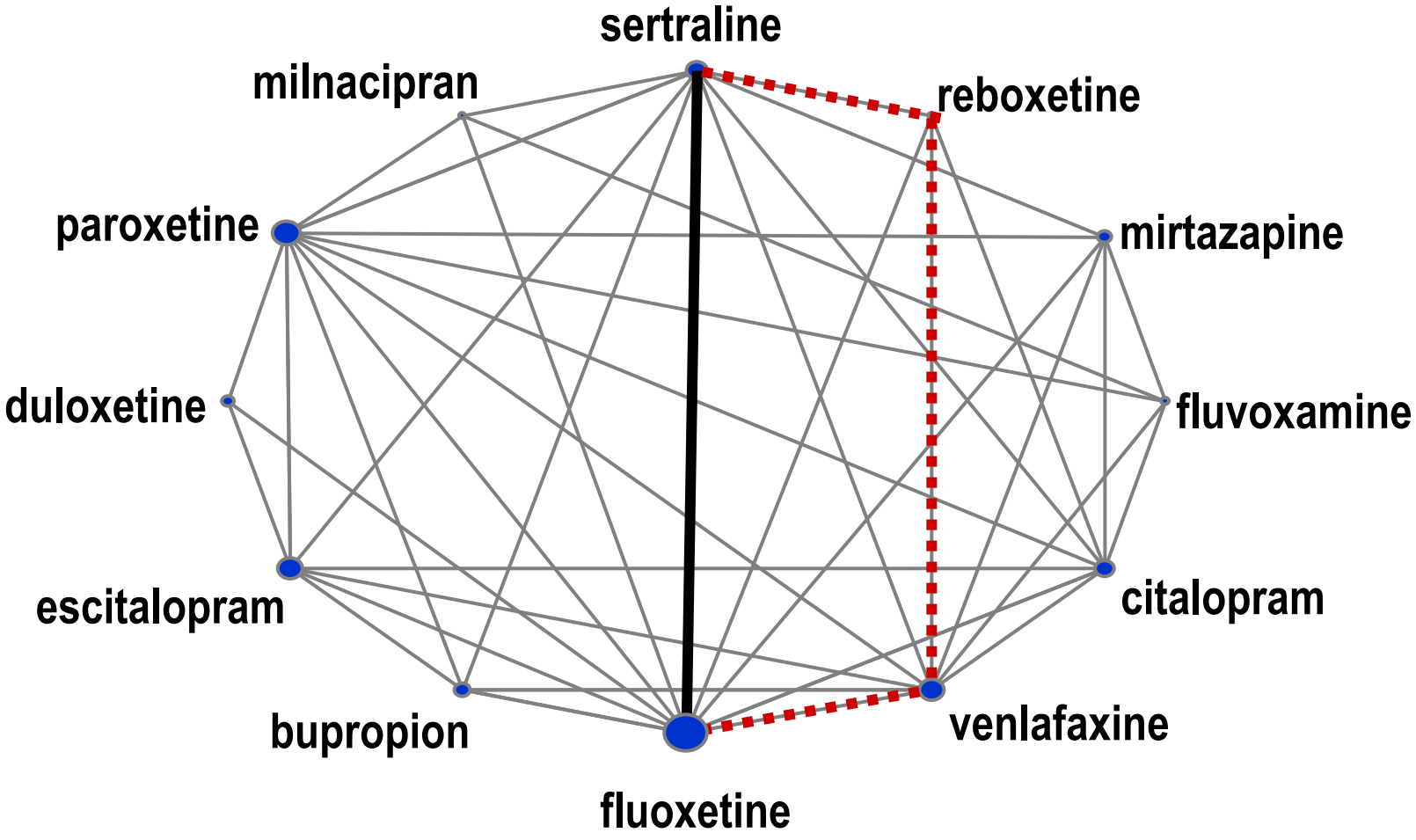


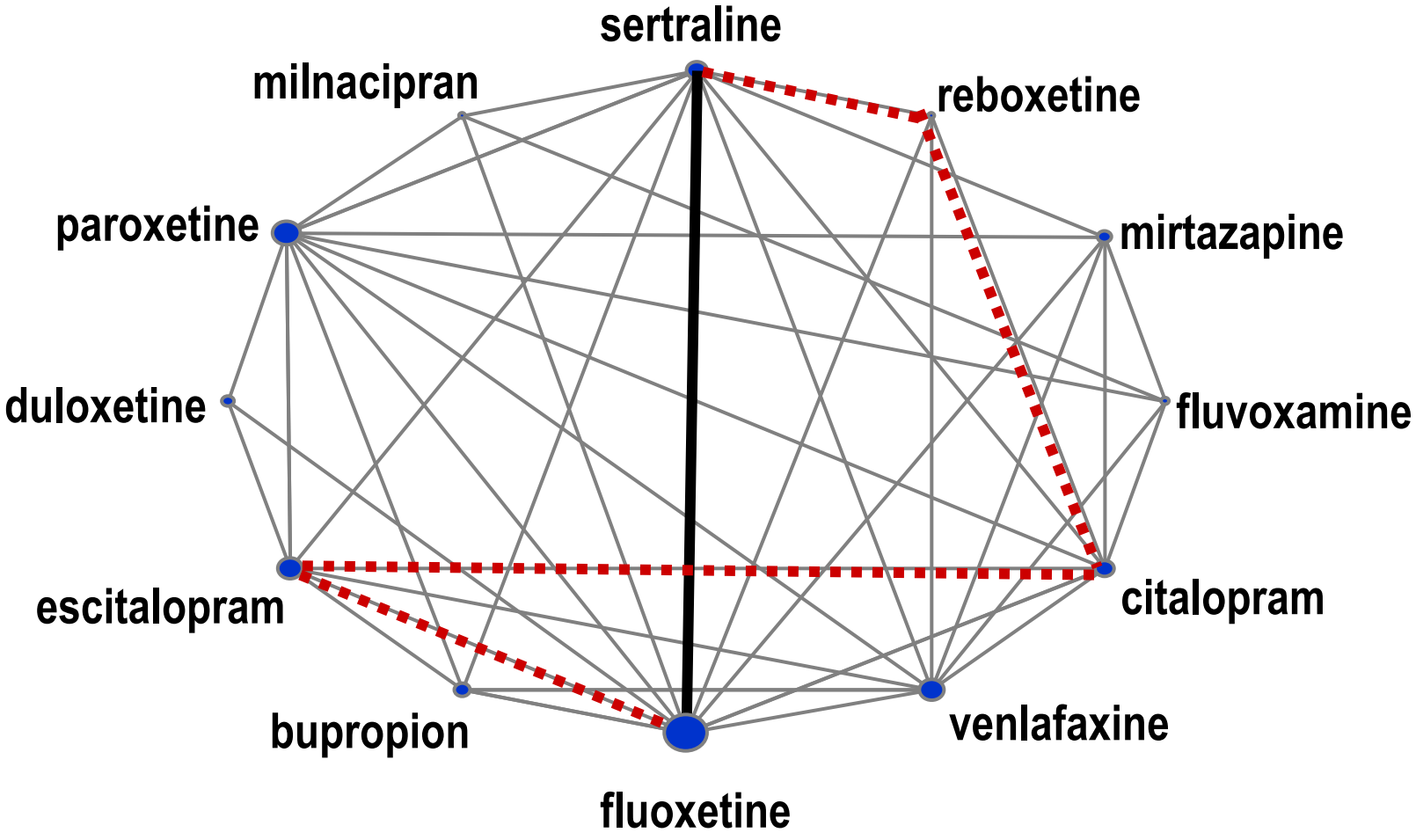
Network of experimental comparisons



Network of experimental comparisons



Network of experimental comparisons



12 new generation antidepressants

several meta-analyses have been published

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

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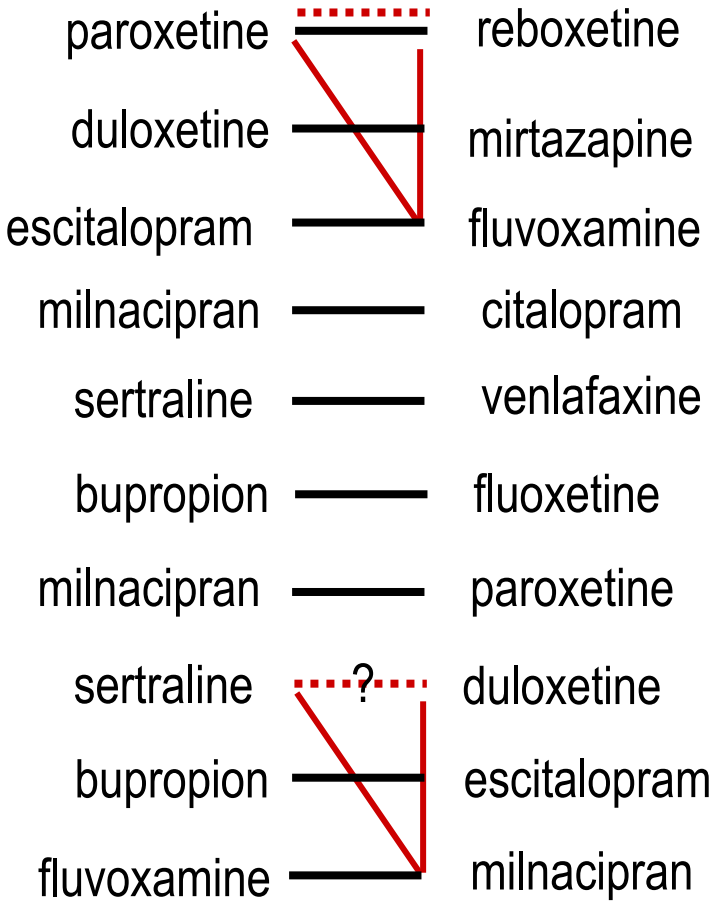


paroxetine	0%
sertraline	7%
citalopram	0%
escitalopram	26%
fluoxetine	0%
fluvoxamine	0%
milnacipran	1%
venlafaxine	11%
reboxetine	0%
bupropion	0%
mirtazapine	54%
duloxetine	0%

Probability to be the best

Current meta-analysis misses data!

Benefits of NMA

Network meta-analysis (NMA)

- synthesizes direct and indirect evidence in a network of trials that compare multiple interventions

Advantages

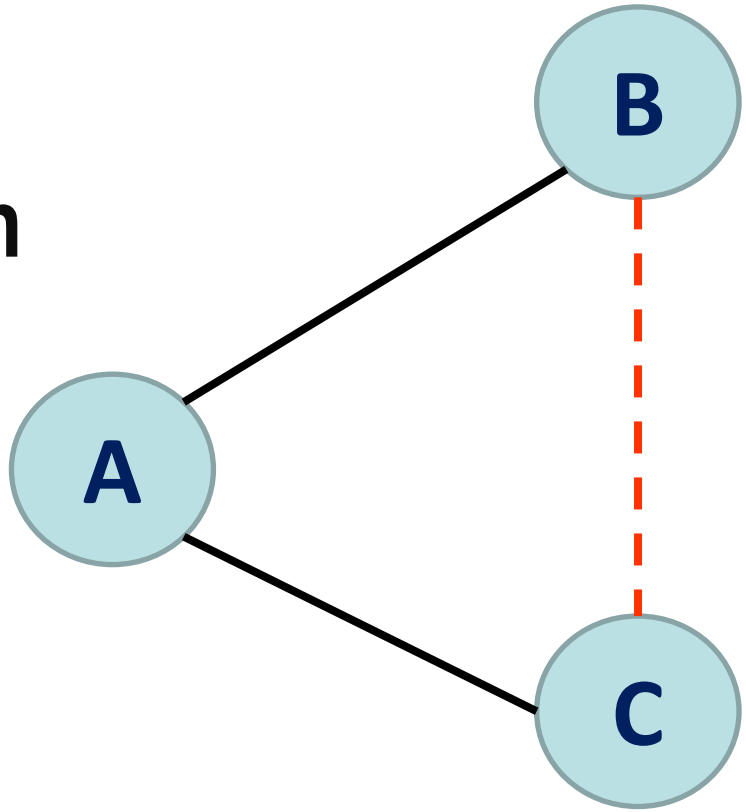
- enables drawing inference for treatment comparisons never appeared in individual studies
- usually gives estimates with increased precision compared to pairwise meta-analysis
- provides an estimate of the treatment relative ranking according to the studied outcome

Criticism of indirect evidence

- Indirect comparisons provide observational results because the treatments being compared have not been randomized across trials
- Differences in patient characteristics at baseline or in effect modifiers across treatment comparisons
- Indirect comparisons are valid if the distribution of effect modifiers does not differ across trials (the intervention effects are transitive)
- Is direct evidence preferable to indirect evidence?
- Shall we use indirect comparison only in the absence of direct evidence?

Transitivity

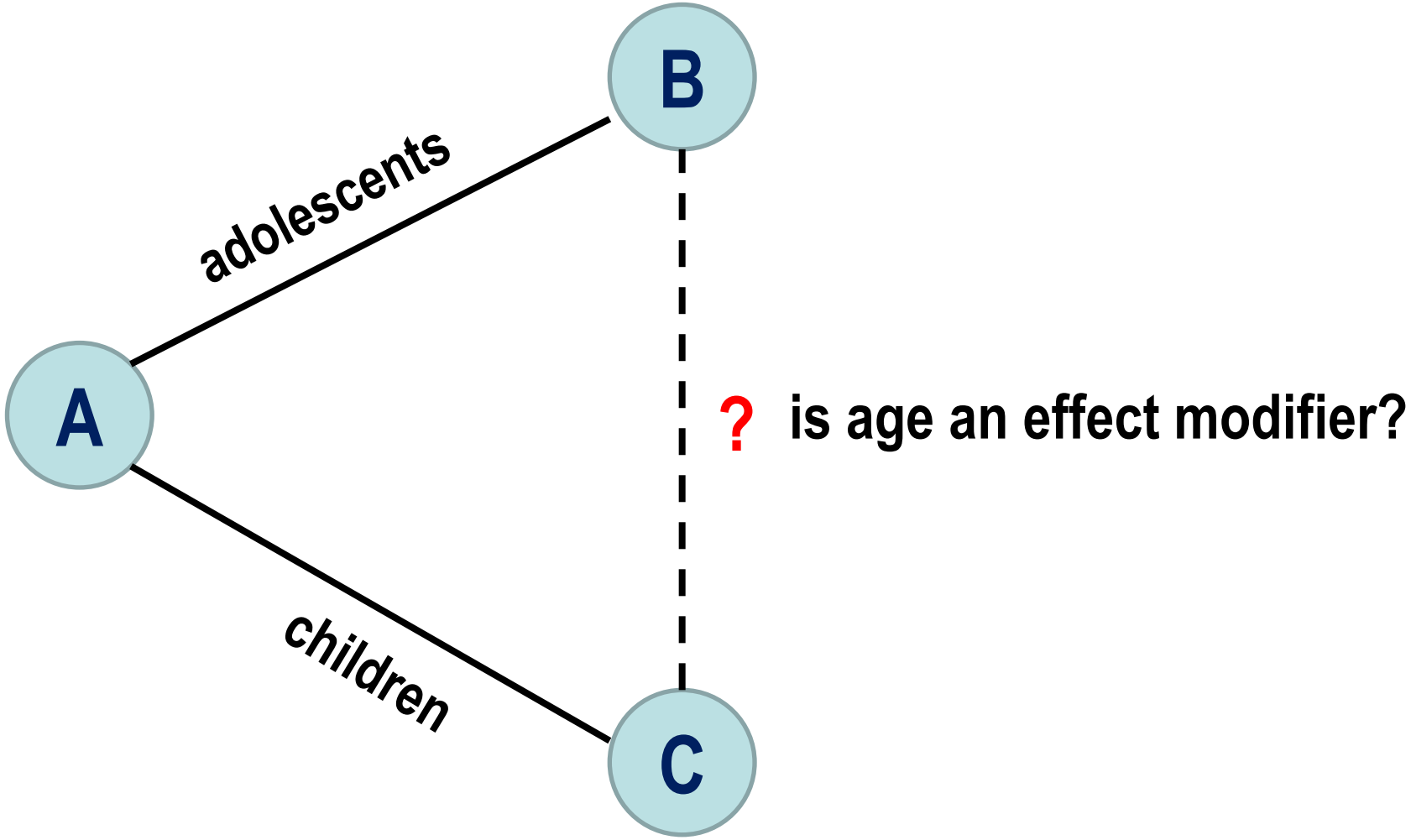
Untestable assumption



The anchor treatment A is 'transitive'

….but you can evaluate clinically and epidemiologically its plausibility

Validity of indirect comparisons



The treatment comparisons have not been randomized across studies

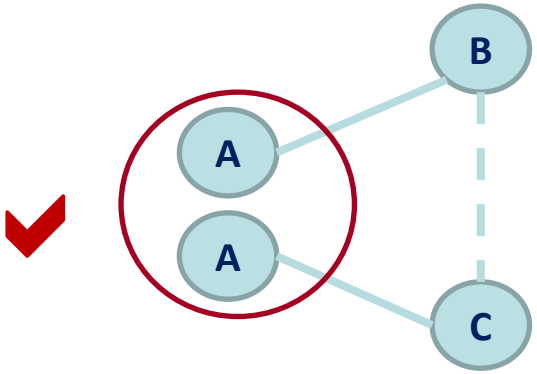
- In an ABC network you may have invalid indirect comparisons if AB studies and AC studies differ considerably

AB comparisons	AC comparisons
before 1990	after 1990
developed countries	developing countries
children	adolescents
low baseline risk	high baseline risk
short period of time	long period of time
A is implemented in a conventional way	A is implemented in a modern way

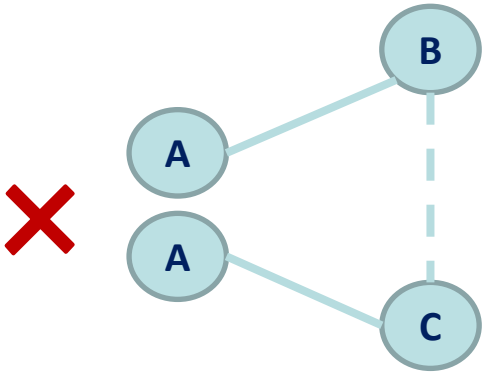
Transitivity

- Transitivity refers to the genuine ability to learn about a pairwise comparison via an intermediate treatment via an indirect root
- It requires the intermediate treatment to be equivalent when compared against each of the treatments of interest
- It requires that studies contributing to the indirect comparison do not differ in important ways

Transitivity requires…

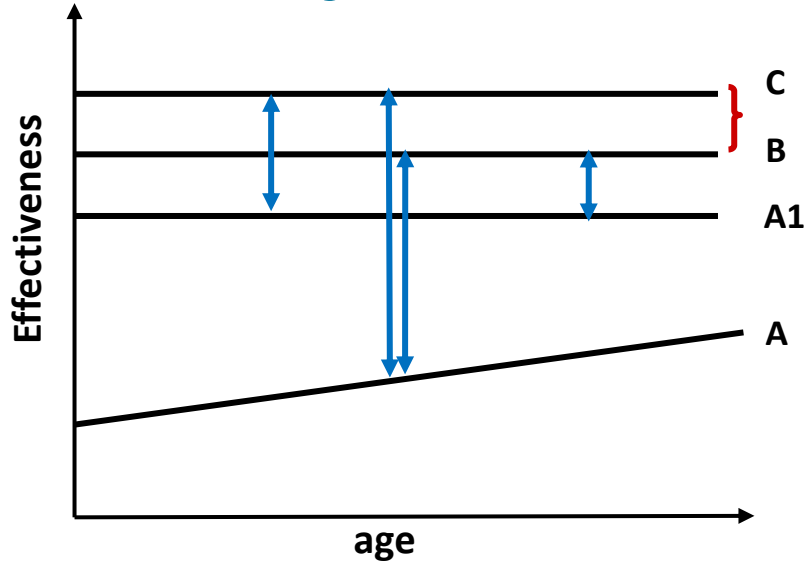


- the ‘anchor’ treatment A to be similarly defined when it appears in AB and AC trials. e.g. a treatment given at different doses but no systematic difference in the *average* dose of A across AB and AC comparison

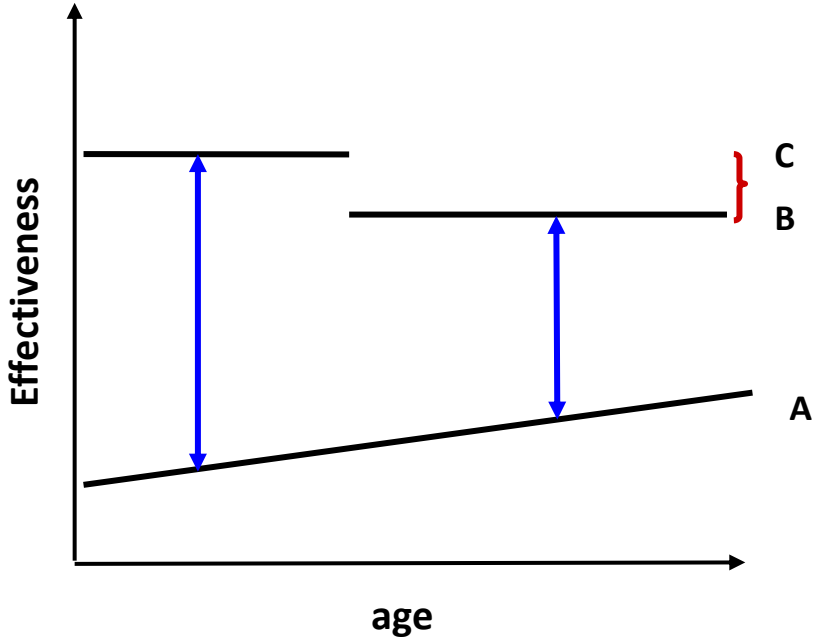


- the ‘anchor’ treatment A may be different in AB and AC studies e.g. a pharmacological placebo may not be identical in terms of effectiveness to a non-pharmacological placebo

Transitivity means...



...that AC and AB trials do not differ with respect to the distribution of effect modifiers



Difficult to defend when you have older and newer treatments

Consistency

- Statistical manifestation of transitivity

- The consistency assumption states that direct and indirect evidence should be in agreement.

- Check the consistency assumption
  - Estimate the disagreement between direct and indirect evidence

What is inconsistency

- ***Consistency*** = The data fit together according to the laws of transitivity
  - i.e. for each pair of interventions A and B, all sources of evidence about A vs B agree with each other

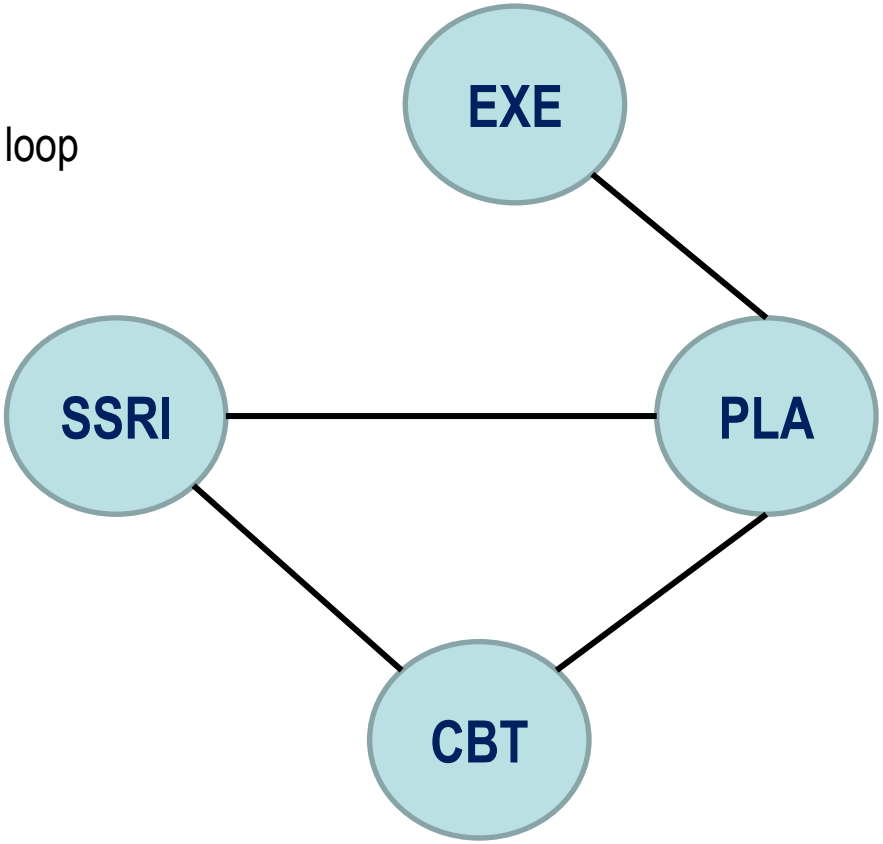
    (this means direct evidence, if available, and different routes to indirect evidence)

- ***Inconsistency*** = Lack of consistency
- Only ***closed loops*** can tell us about (in)consistency
- NMA models that relax the consistency assumption have been developed

Example: CBT vs SSRI vs exercise vs placebo

can assess consistency in the closed loop

can assess transitivity everywhere



Comparison	SMD	CIs	S.E.
Placebo vs CBT	-0.34	(-0.41, -0.28)	0.03
Placebo vs SSRI	-0.19	(-0.30, -0.10)	0.05
Placebo vs exercise	-0.23	(-0.31, -0.15)	0.04

Inconsistency Factor

Indirect $SMD^{ind}_{SSRIvsCBT} = -0.15$

$var\left(SMD^{ind}_{SSRIvsCBT}\right) = 0.004$

Direct $SMD^{dir}_{SSRIvsCBT} = 0.04$

$var\left(SMD^{dir}_{SSRIvsCBT}\right) = 0.011$

$$IF = \left|SMD^{dir}_{SSRIvsCBT} - SMD^{ind}_{SSRIvsCBT}\right| = |0.04 - (-0.15)| = 0.19$$

$$var(IF) = var\left(SMD^{dir}_{SSRIvsCBT}\right) + var\left(SMD^{ind}_{SSRIvsCBT}\right) = 0.004 + 0.011 = 0.015$$

You can do this with any measure... lnOR, lnRR, RD, mean difference, HR e.t.c

How much inconsistency?

$$z = \frac{IF}{\sqrt{var(IF)}} \sim N(0,1)$$

95% Confidence Interval for inconsistency

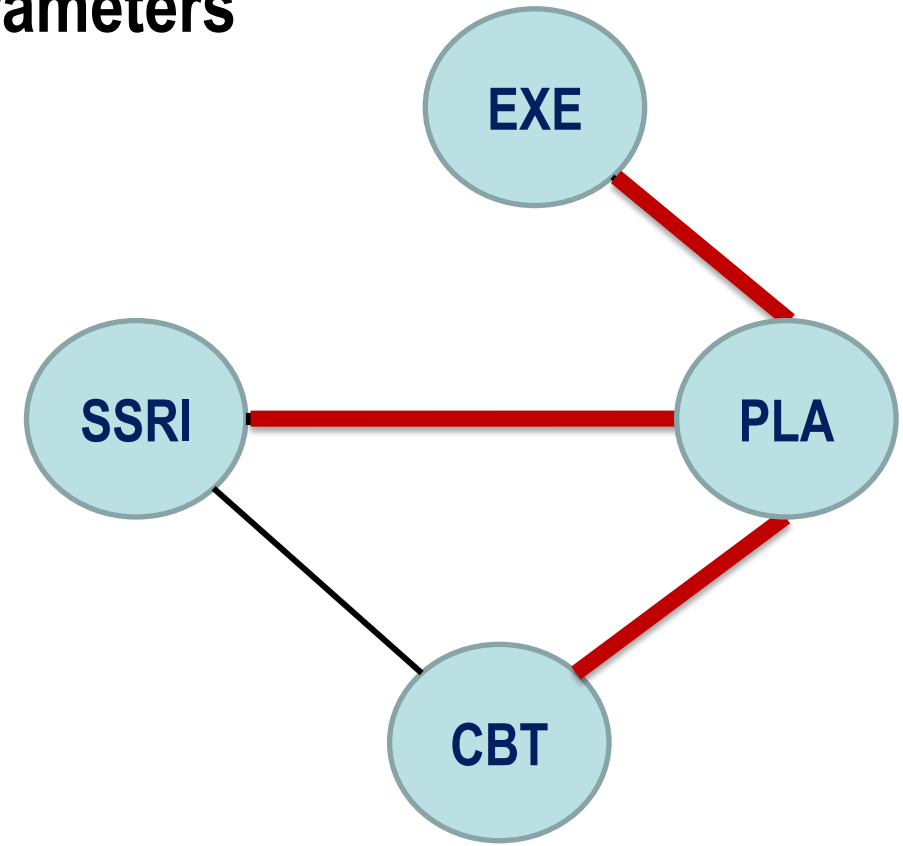
$$IF \pm 1.96\sqrt{var(IF)}$$

$$0.19 \pm 1.96\sqrt{0.015}$$

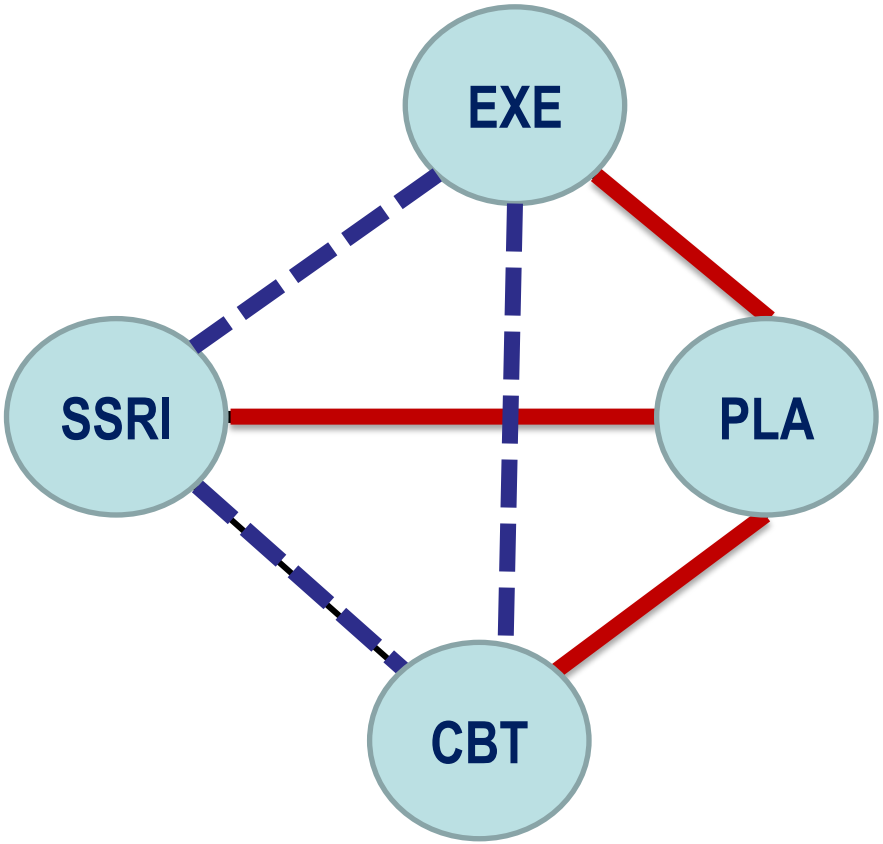
$$(-0.05, 0.43)$$

Estimating the model

- choose a reference treatment
- choose basic parameters



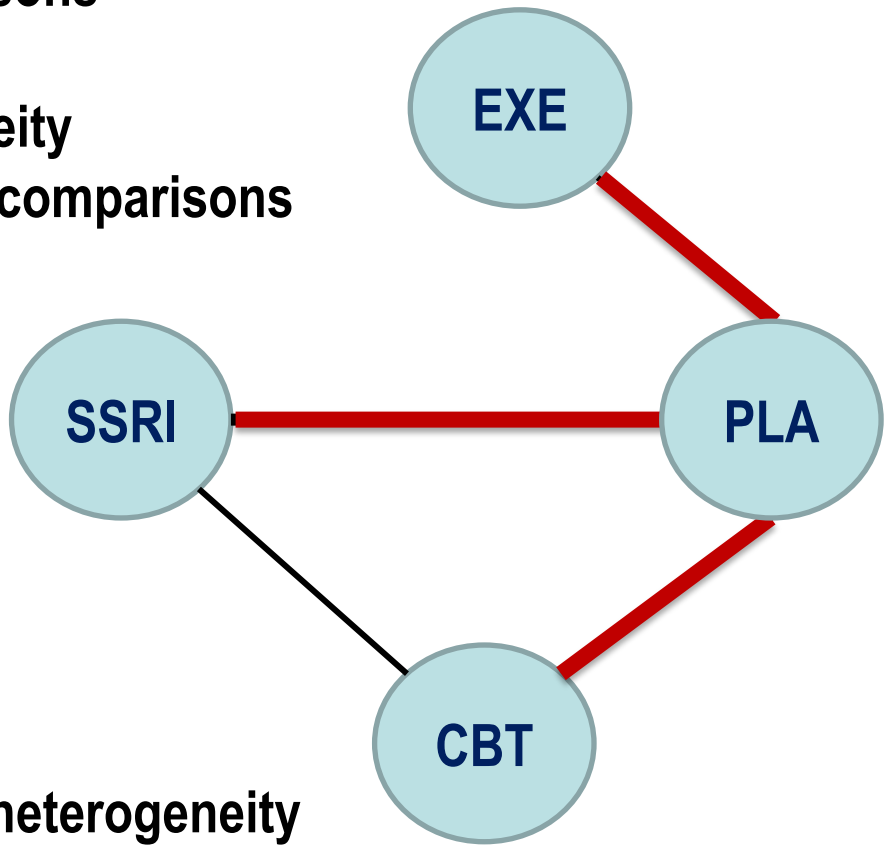
Estimating the model – functional parameters



Estimating the model – basic parameters

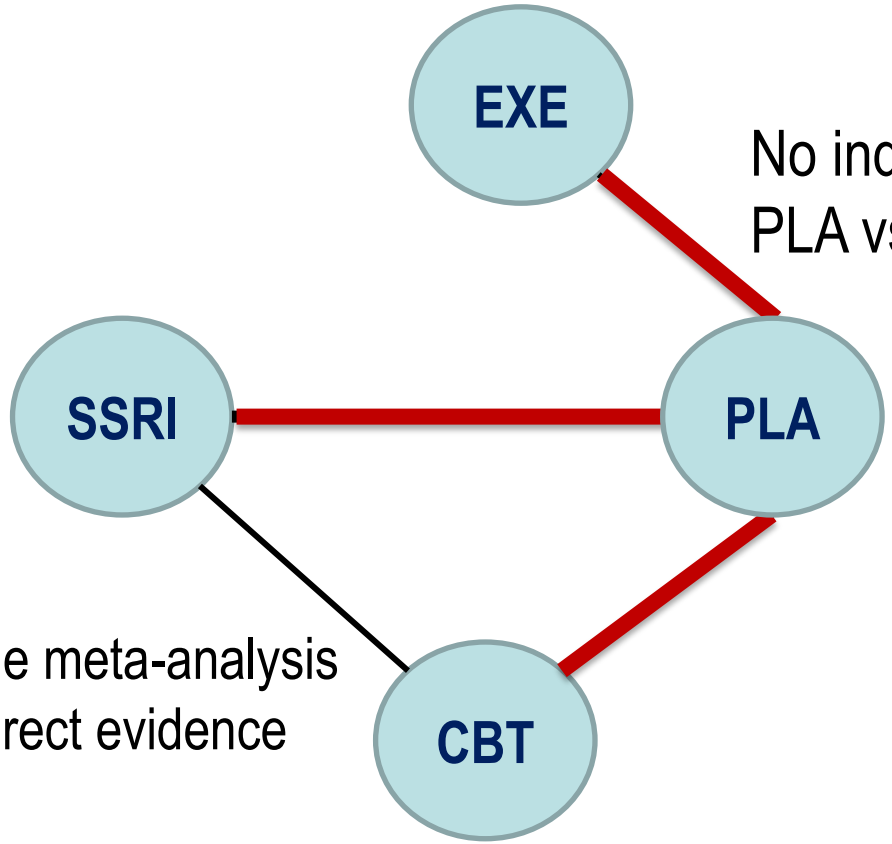
There are four direct comparisons

Usually a common heterogeneity
is assumed across treatment comparisons



With T treatments we need to
estimate T-1 parameters and heterogeneity

Estimating the model – basic parameters



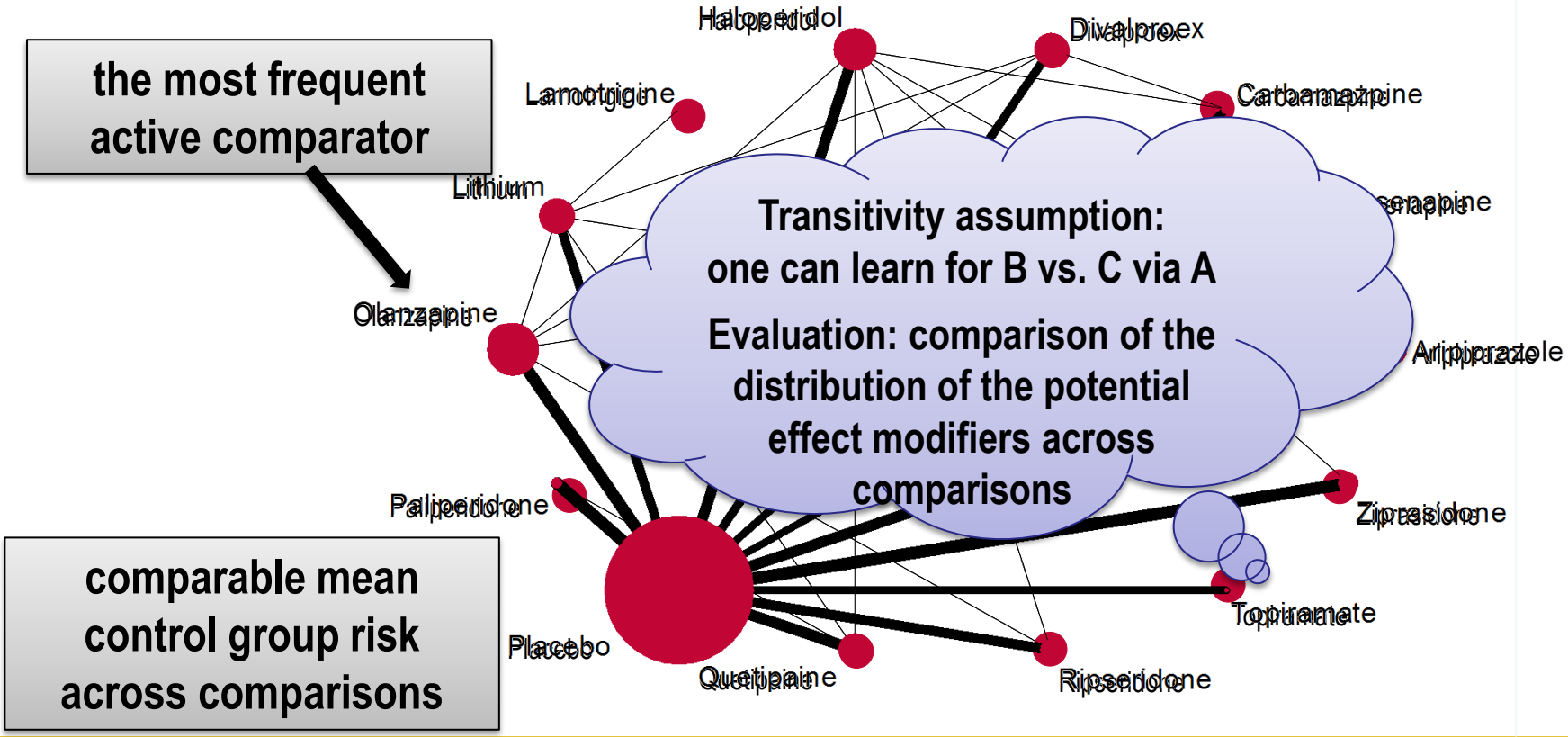
No indirect evidence for PLA vs EXE

Results between NMA and simple meta-analysis may differ even if there is no indirect evidence because of the assumption of common heterogeneity across comparisons

Understanding & presenting the evidence base

Network plot/diagram (STATA command `networkplot`)

- visual representation of the network structure
- concise description of its characteristics – use of weighting schemes



Understanding & presenting the evidence base

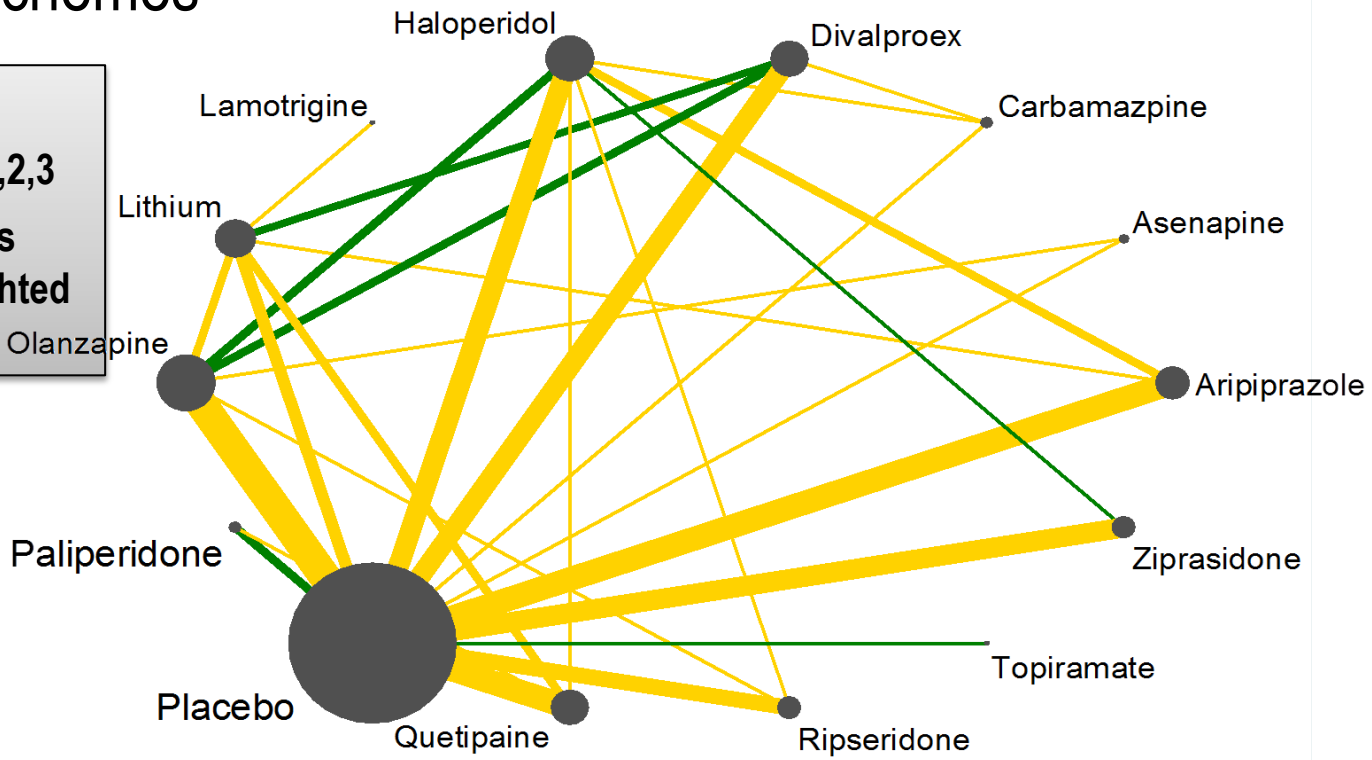
Network plot/diagram (STATA command `networkplot`)

- risk of bias → important study-level characteristic
- some comparisons may include trials with design limitations – use of coloring schemes

Allocation concealment

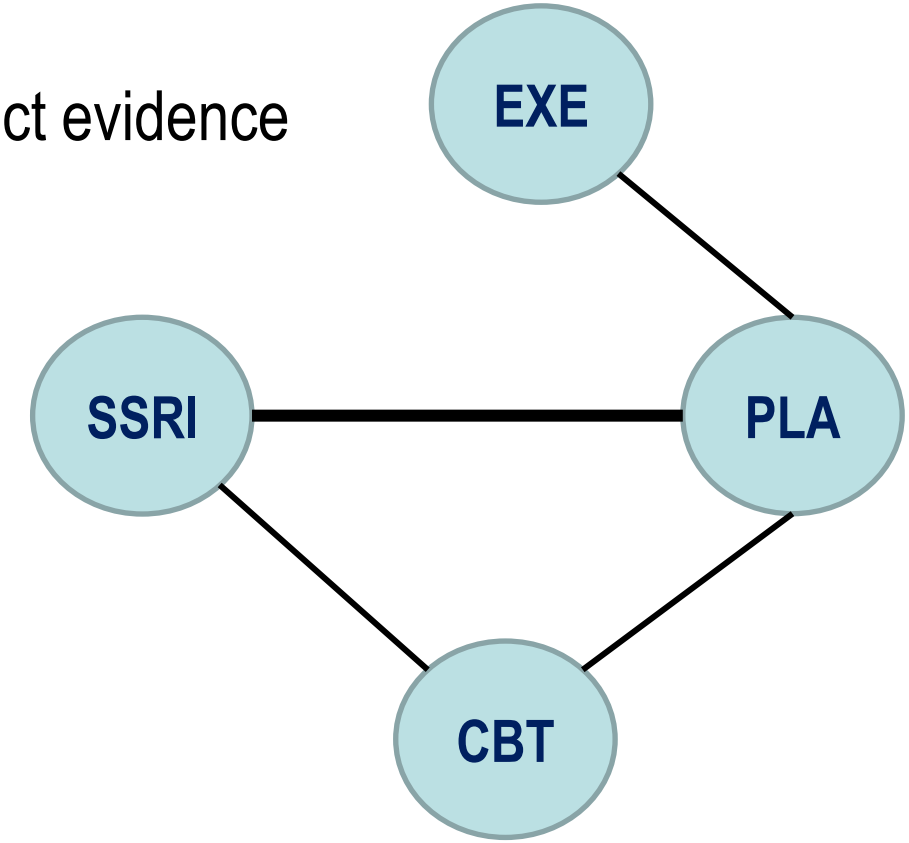
Study-specific bias level=1,2,3

Comparison-specific bias level=inverse variance weighted average



Understanding & presenting the evidence base

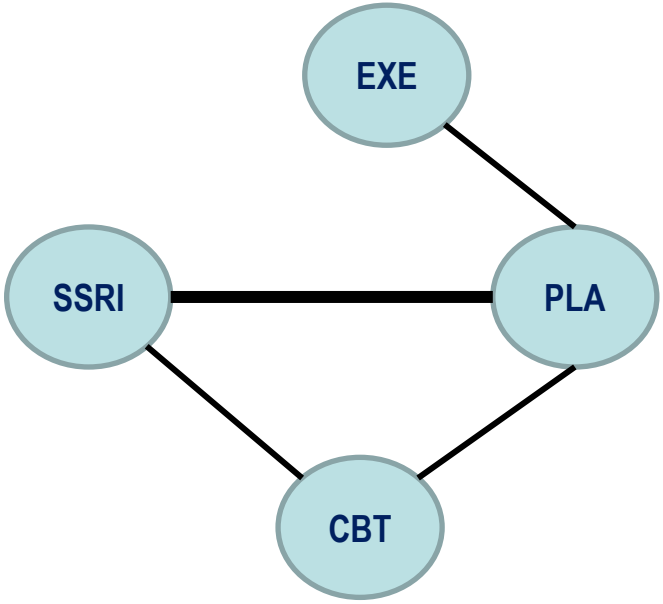
- How much each direct comparison contributes to the entire network
- How much each direct comparison contributes to each network summary estimate
- How much is the contribution of indirect evidence



Understanding & presenting the evidence base

Contribution plot/diagram (STATA command `netweight`)

- Identify the most influential comparisons in the network



		Direct comparisons in the network			
		PLA vsEXE	PLA vsCBT	PLA vsSSRI	CBTvsSSRI
Network meta-analysis estimates	Mixed estimates				
	PLA vs EXE	100.0			
	PLA vs CBT		68.0	16.0	16.0
	PLA vsSSRI		29.5	41.0	29.5
	CBTvsSSRI		28.1	28.1	43.7
	Indirect estimates				
	EXE vs CBT	45.7	37.0	8.7	8.7
	EXE vsPTCA	41.4	17.3	24.1	17.3
Entire network		31.2	29.6	20.2	19.0
Included studies		16	3	33	10

Evaluating & presenting the assumptions

Inconsistency plot (STATA command `ifplot`)

- estimation in NMA relies on the consistency assumption

$$\mu_{YZ} = \mu_{XZ} - \mu_{XY}$$

- violation of consistency is an important threat for the validity of the results

Evaluating & presenting the assumptions

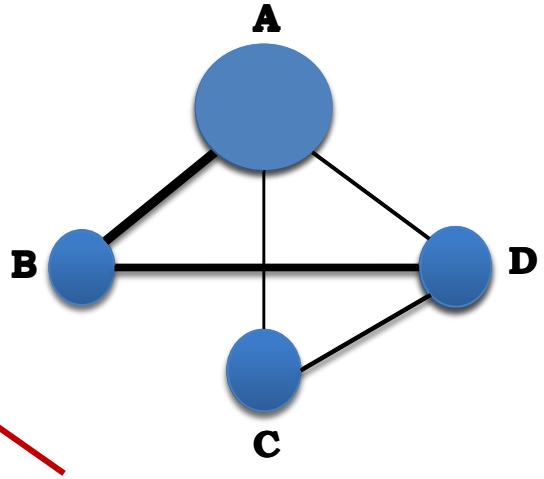
Inconsistency plot (STATA command `ifplot`)

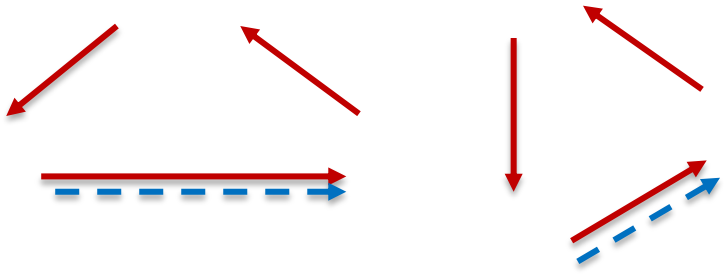
- loop-specific approach → look at each closed loop in the network separately
- estimate the absolute difference between the direct and the indirect estimate for one comparison

$$\hat{\mu}^{dir} - \hat{\mu}^{ind} = \widehat{IF}$$

$$H_0: IF = 0$$

$$exp(\widehat{IF}) = ROR$$

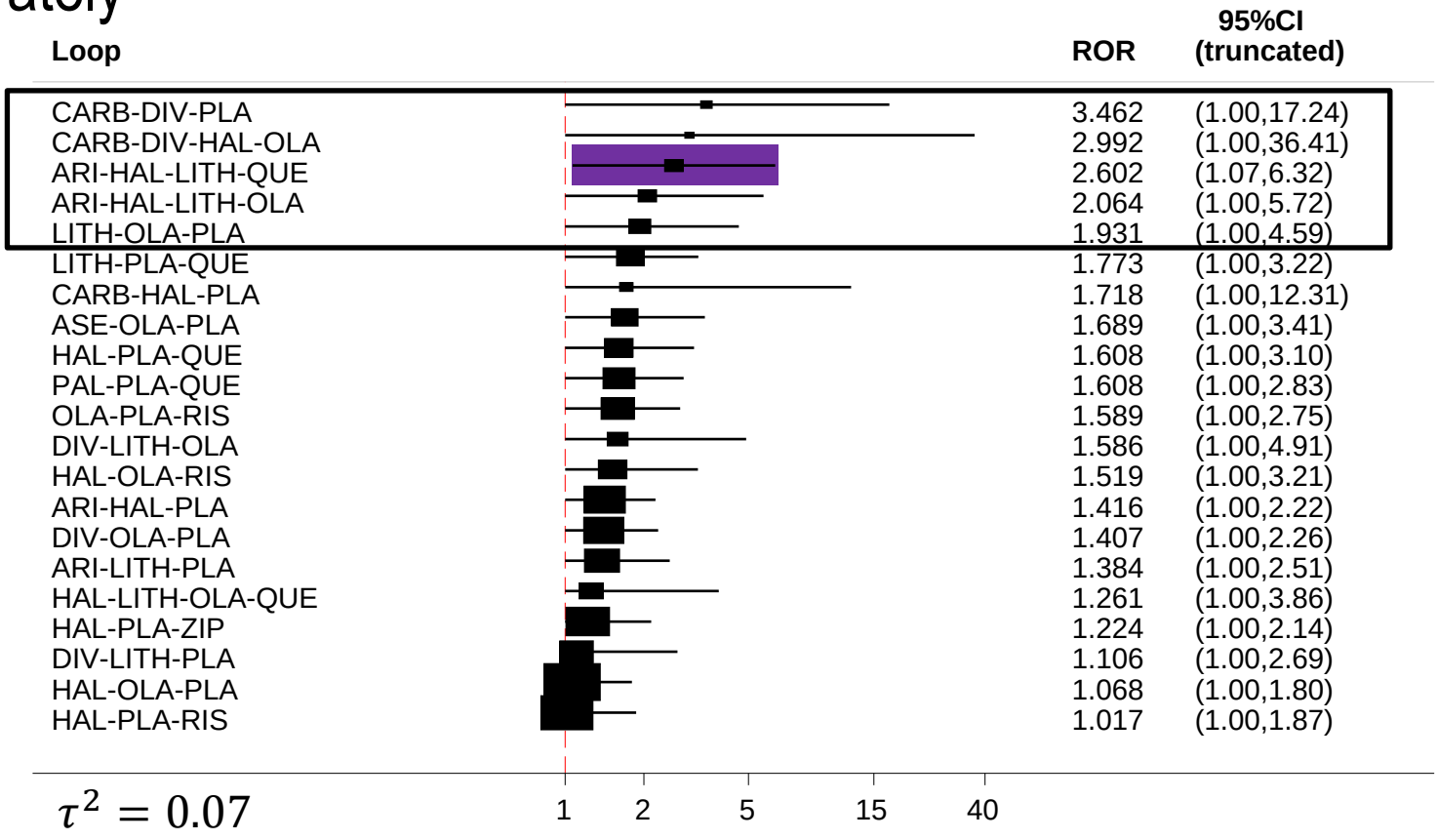




Evaluating & presenting the assumptions

Inconsistency plot (STATA command `ifplot`)

- loop-specific approach → look at each closed loop in the network separately



Presenting the results & drawing conclusions

Ranking probabilities (STATA command sucra)

- ranking probability⟶ the probability for a treatment of being at a particular rank

$$p_{rt} = \frac{\#\ simulations\ (t = r)}{total\ \#\ simulations}$$

- inference on relative ranking should account for the uncertainty in ranking

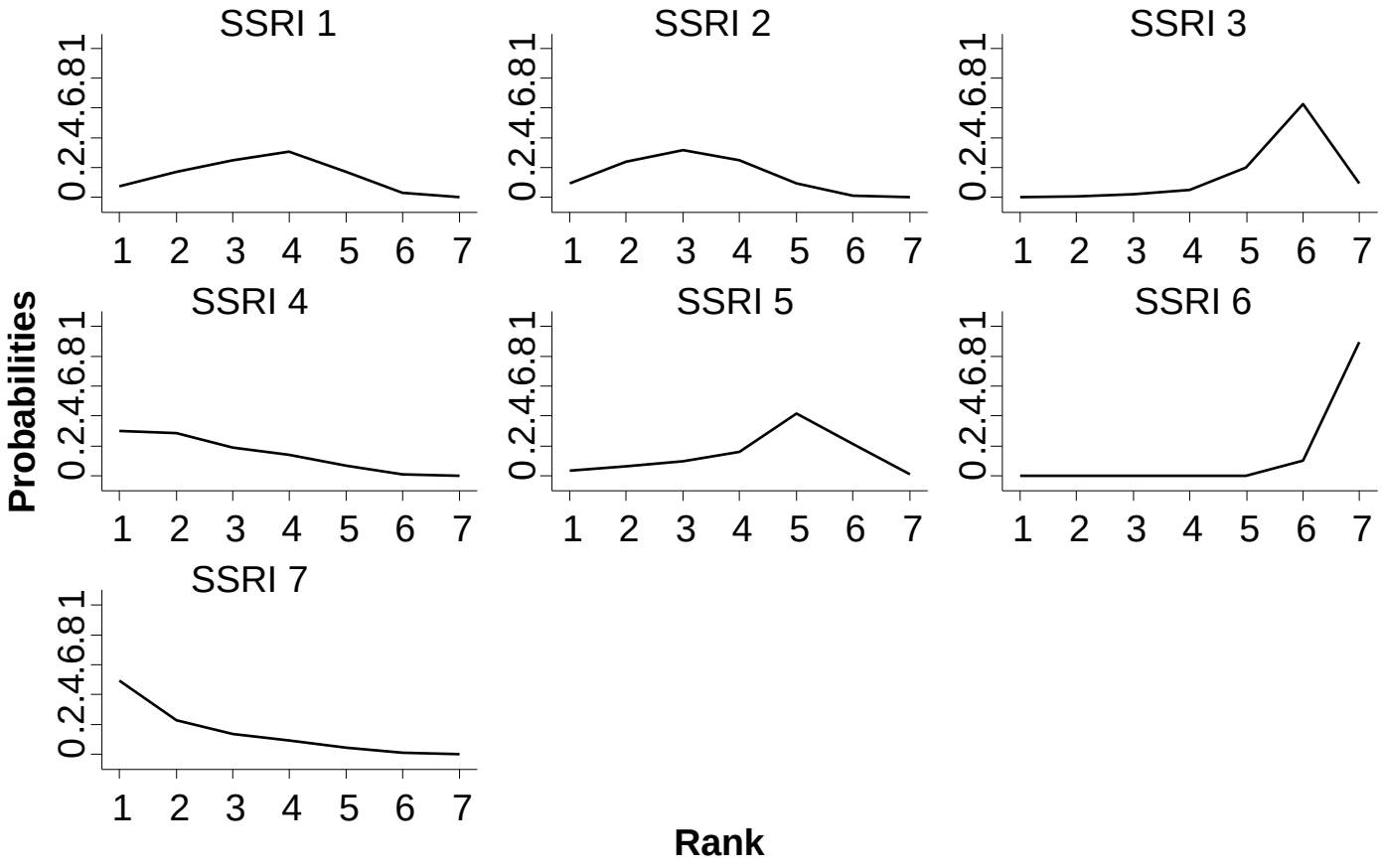
conclusions based on the probability of being best often are misleading

- show the entire distribution of the ranking probabilities

Presenting the results & drawing conclusions

Ranking probabilities (STATA command `sucra`)

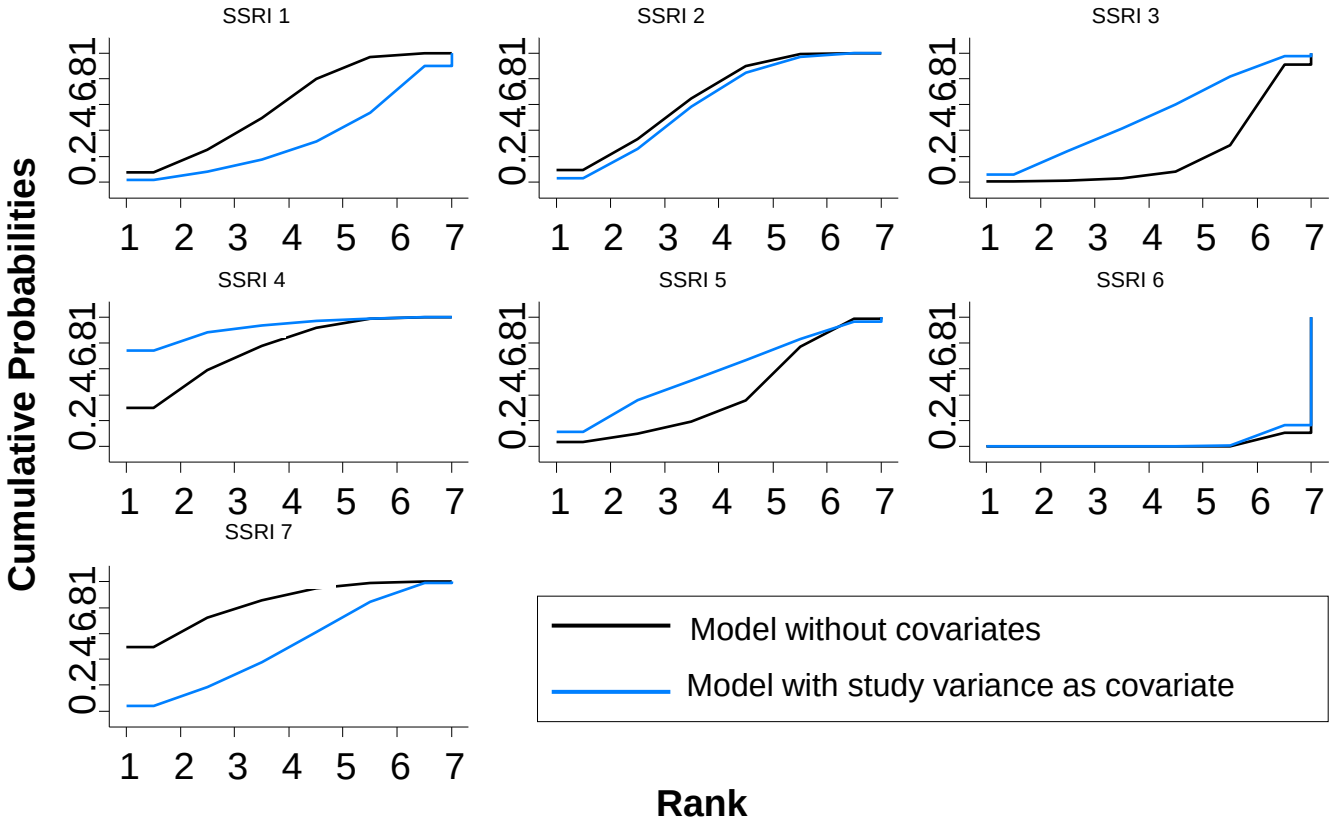
- draw the rankograms for all competing treatments in the network



Presenting the results & drawing conclusions

Ranking probabilities (STATA command `sucra`)

- cumulative ranking probability → the probability for a treatment of being within the first r places



Presenting the results & drawing conclusions

Relative ranking for two outcomes (STATA command `clusterank`)

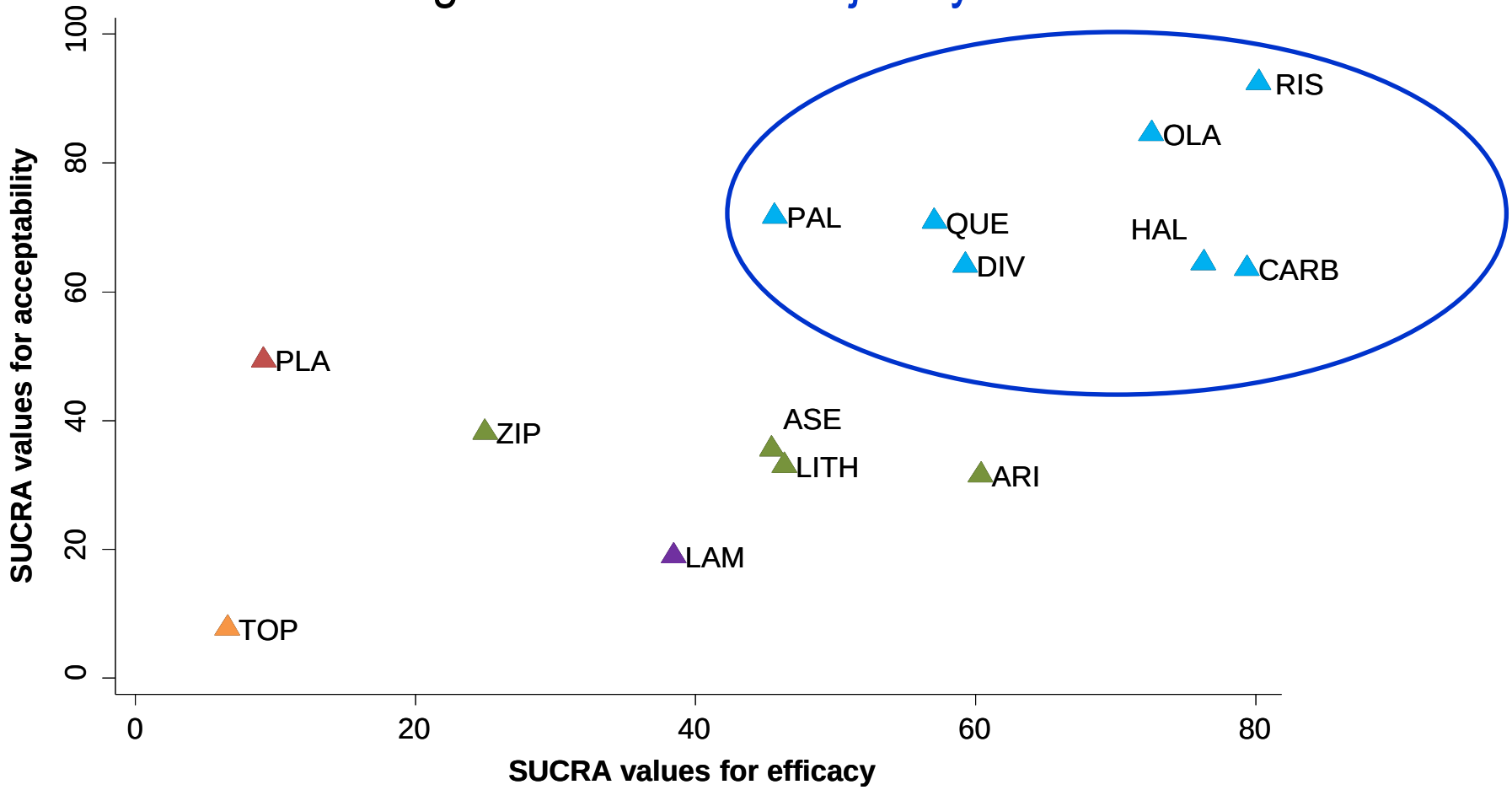
- decision-making with respect to which interventions should be recommended should account for several factors

	Efficacy		Acceptability			Efficacy		Acceptability	
ARI	60.2	5	32.4	12	**OLA**	72.4	4	85.5	2
ASE	45.3	11	36.4	10	**PAL**	45.5	10	72.6	4
CARB	79.2	2	64.5	7	**PLA**	9.00	14	50.3	8
DIV	59.1	7	65.0	14	**QUE**	56.9	8	71.8	5
HAL	76.1	3	65.4	6	**RIS**	80.4	1	93.4	1
LAM	38.3	12	19.9	13	**TOP**	6.40	6	8.60	3
LITH	46.2	9	33.9	11	**ZIP**	24.8	13	39.1	9

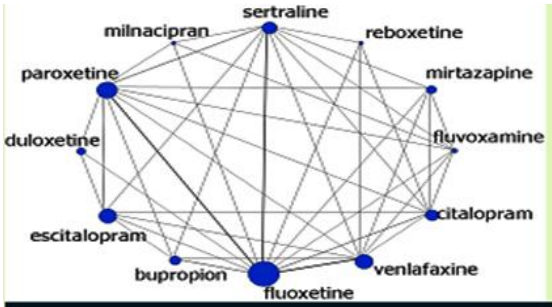
Presenting the results & drawing conclusions

Relative ranking for two outcomes (STATA command `clusterank`)

- present the relative ranking for two outcomes jointly



mtm.uoi.gr



Multiple-Treatments Meta-Analysis

A Framework for Evaluating and Ranking Multiple Healthcare Technologies

You are here: Home

- HOME
- TUTORIAL and BIBLIOGRAPHY
- HOW TO DO AN MTM
- IMMA ERC starting Grant
- RESEARCH and PUBLICATIONS
- STATA routines for Network Meta-Analysis
- Material from Publications (software and protocols)
- Meta-analysis methods and tools
- TEAM
- LINKS
- Seminars

Multiple-Treatments Meta-analysis (MTM)

Meta-analysis is the statistical technique used to synthesize evidence from experiments addressing the same research question. It is often used to combine data from clinical trials regarding the relative effectiveness of two interventions in order, for example, to infer about whether antihypertensives A and B are equally effective in lowering blood pressure.
The main drawback of the current state of the art is that meta-analysis focuses on comparing only two alternatives. However, clinicians and patients need to know the relative ranking of a set of alternative options and not only whether option A is better than B.
The statistical methodology applied to synthesize information over a network of comparisons involving all alternative treatment options for the same condition is called **Multiple-Treatments Meta-Analysis**.

This site provides

- **an introduction to statistical and methodological issues related to MTM**
- **links to training material**
- **support to statisticians with the analysis of networks of interventions**
- **ideas and discussions of research in MTM**

References

1) For the **mvmeta** command:

net install mvmeta,from(http://www.mrc-bsu.cam.ac.uk/IW_Stata/meta) replace

2) For NMA routines about **network plots**, **predictive intervals**, **small study effects**, **ranking** and **evaluating inconsistency**:

net install network_graphs, from(http://www.mtm.uoi.gr) replace

1. White IR, Barrett JK, Jackson D, Higgins JPT: Consistency and inconsistency in network meta-analysis : model estimation using multivariate meta-regression. *Research Synthesis Methods* 2012; **3:** 111-125.
2. White IR: Multivariate random-effects meta-regression: Updates to mvmeta. The Stata Journal 2011; **11**(2): 255-270.
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1. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; 331(7521):897-900.
2. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis : many names, many benefits, many concerns for the next generation evidence synthesis school. *Research Synthesis Method* 2012; 3(2):80-97.
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5. Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. BMJ 2013;346
6. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; **23**: 3105-3124.
7. Bucher, H.C., Guyatt, G.H., Griffith, L.E., & Walter, S.D. 1997. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin.Epidemiol.*, 50, (6) 683-691
8. Salanti G, Ades AE, Ioannidis JP. 2011 Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 64(2):163-71

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