Multiple-Treatments Meta-Analysis

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Outline – Part I

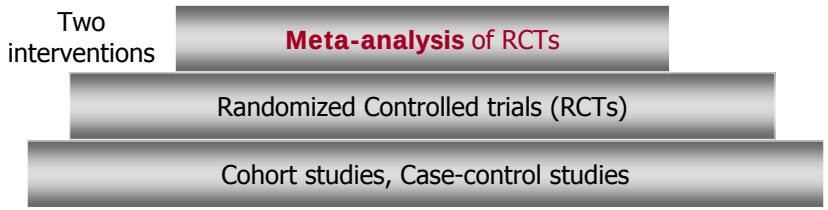
- Concept
- Simple indirect comparison
- Advantages of the methods
- MTM using frequentist meta-regression
- Presentation of results
- The notion of Inconsistency

Outline – Part II

- Bayesian MTM model
- Comparison of models

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

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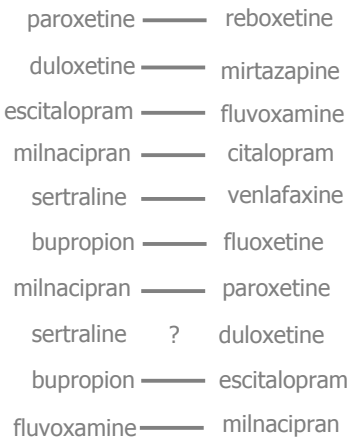

paroxetine	0%
sertraline	7%
citalopram	0%
escitalopram	26%
fluoxetine	0%
fluvoxamine	0%
milnacipran	1%
venlafaxine	11%
reboxetine	0%
bupropion	0%
mirtazapine	54%
duloxetine	0%

Probability to be the best

12 new generation antidepressants

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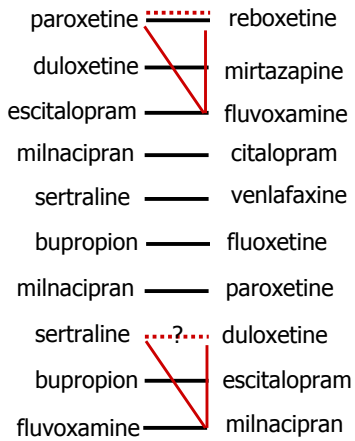

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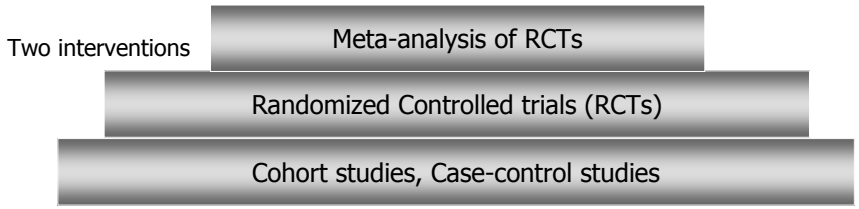
mirtazapine	54%
duloxetine	0%

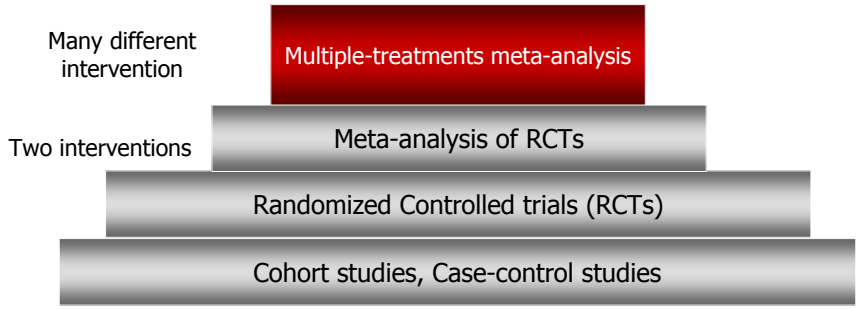
Probability to be the best

Current meta-analysis misses data!

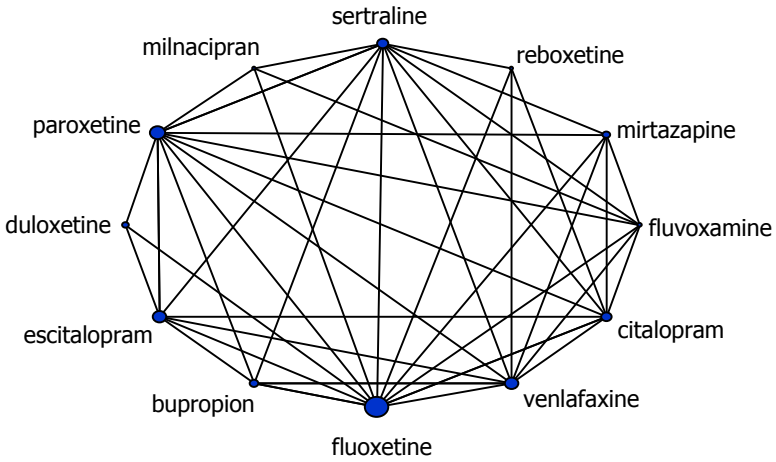
A new methodological framework



A new methodological framework

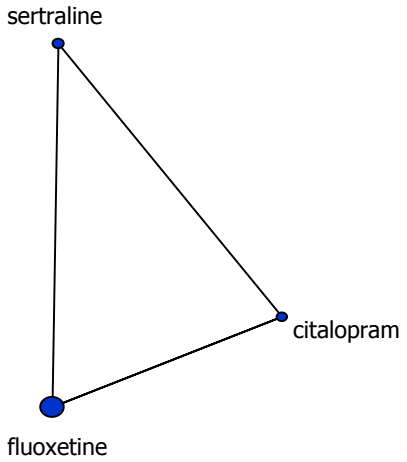


Network of experimental comparisons



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

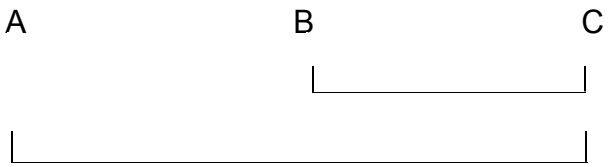
Network of experimental comparisons



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

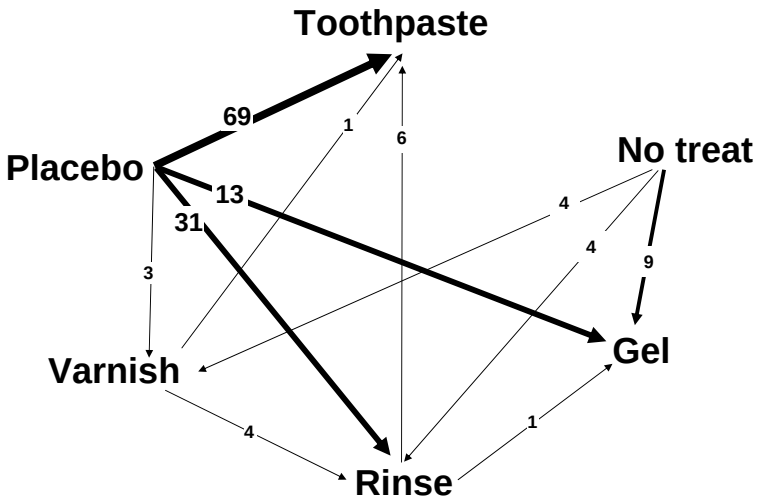
Indirect comparison

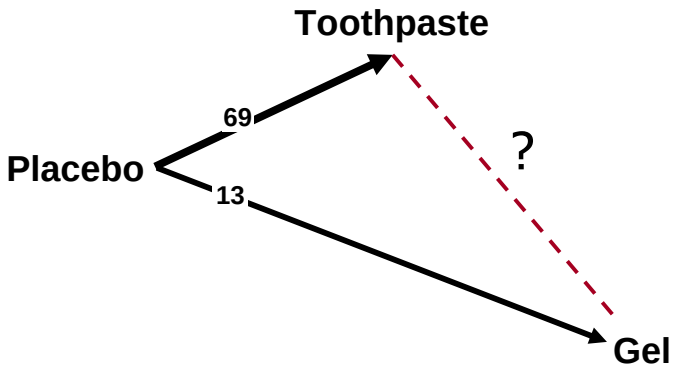
- We can obtain an *indirect* estimate for A vs B from RCTs comparing A vs C and B vs C:



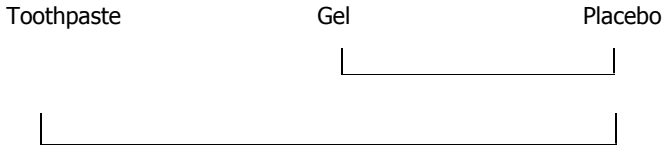
$$MD_{AB} = MD_{AC} - MD_{BC}$$

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





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

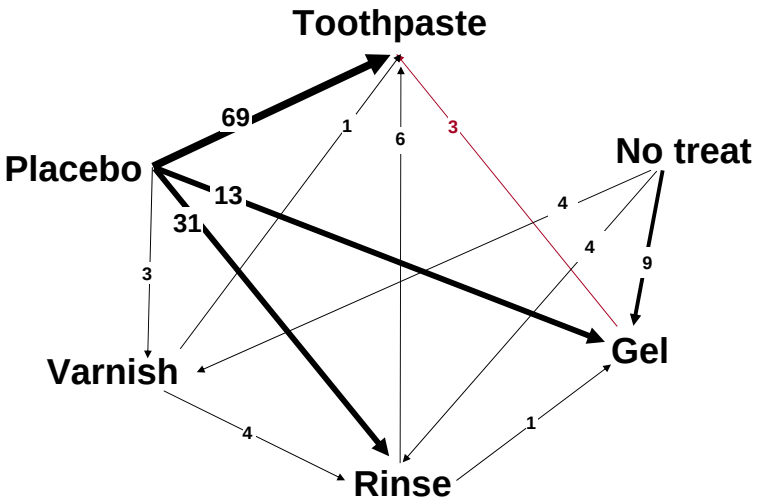
Variance MD_{GvsT} = ((-0.10– (-0.30))/3.92)^2 =0.0026

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)



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

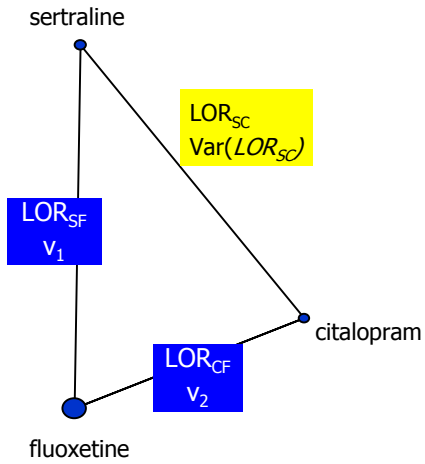
You can do this with any measure... lnOR, lnRR, RD, mean difference, HR, Peto's lnOR etc…

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

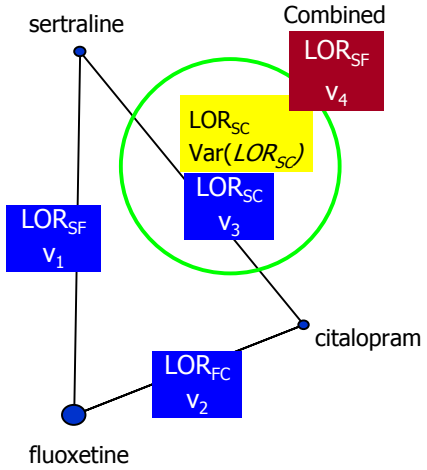
LOR_{SC} = LOR_{SF} - LOR_{CF}

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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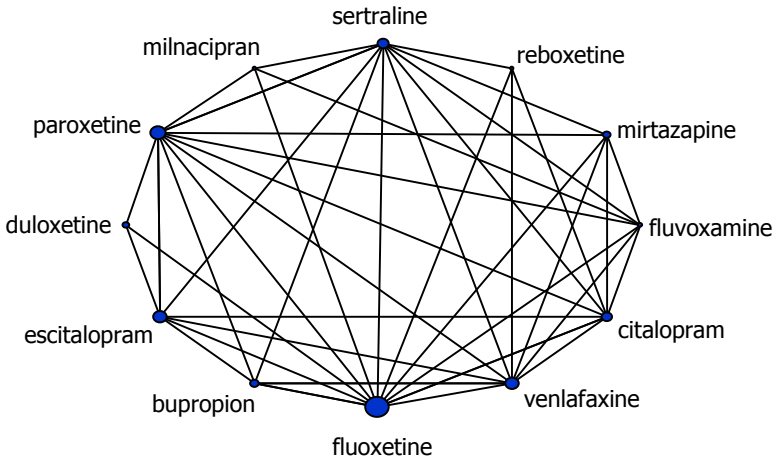
Network of experimental comparisons



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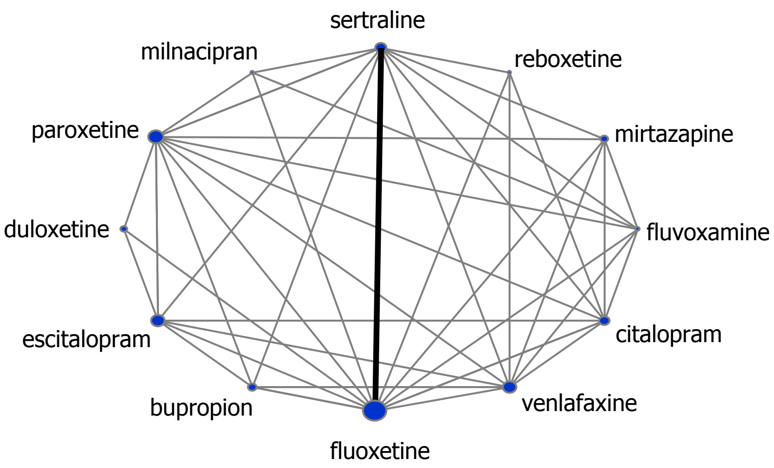

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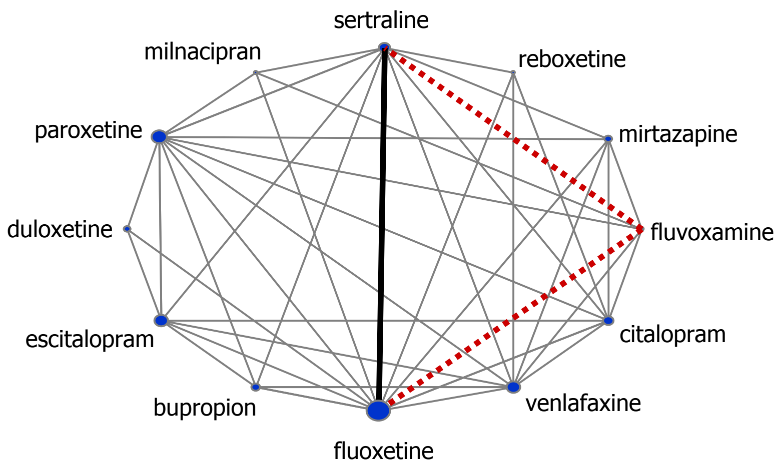

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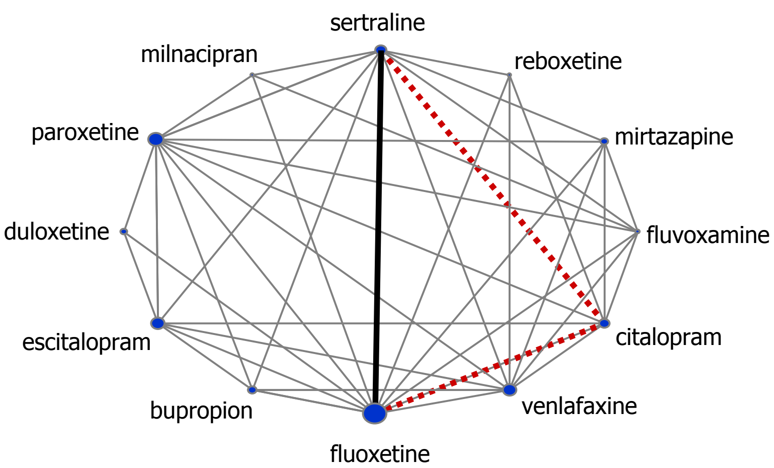

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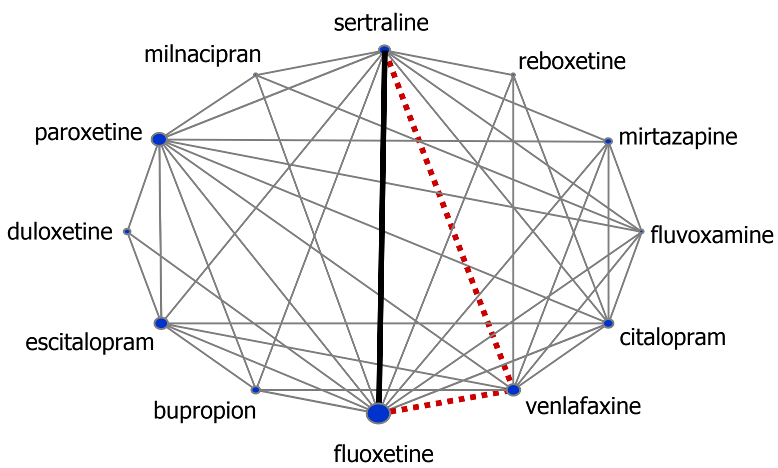
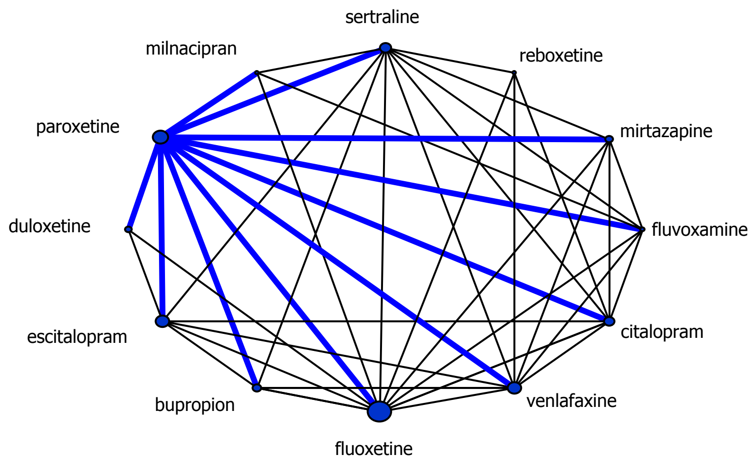
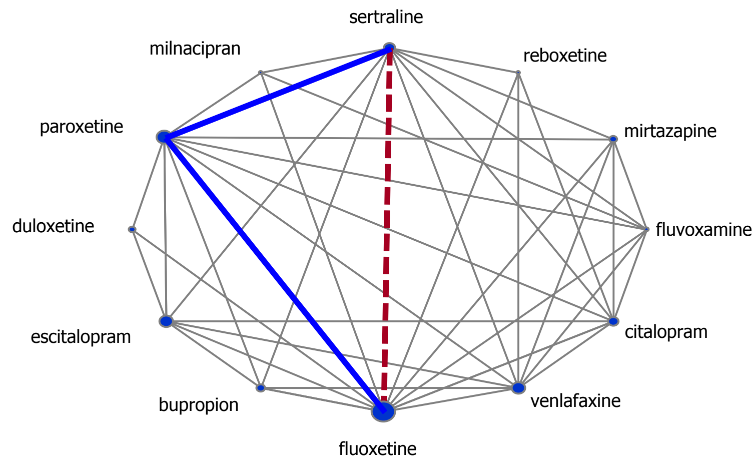


***Lancet* 2009** *Cipriani, Fukurawa, Salanti et al*

Choose basic parameters



All other contrasts are functional!



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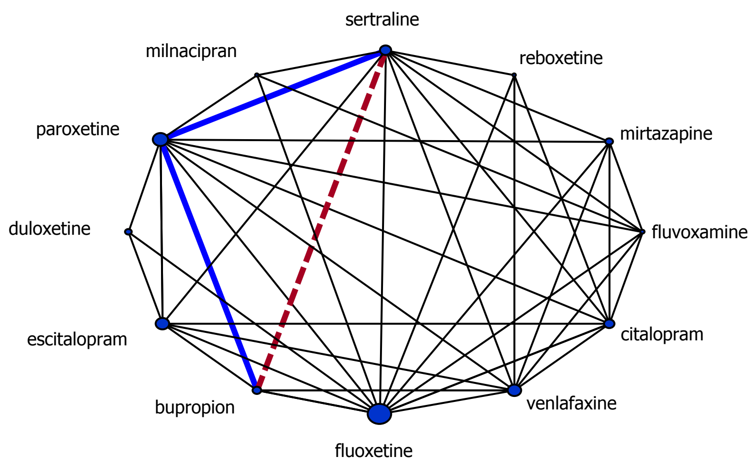

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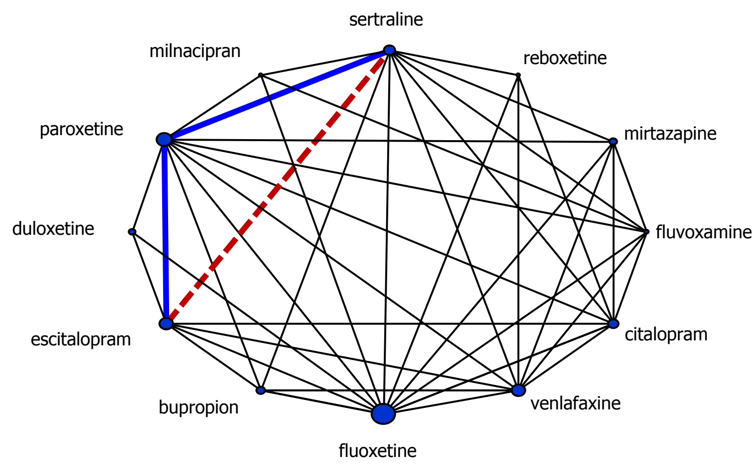
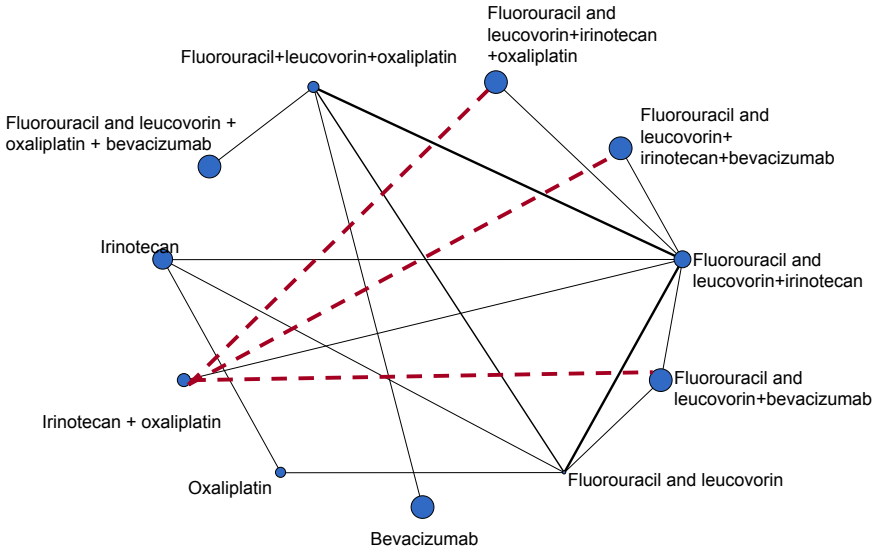


Advantages of MTM

- 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

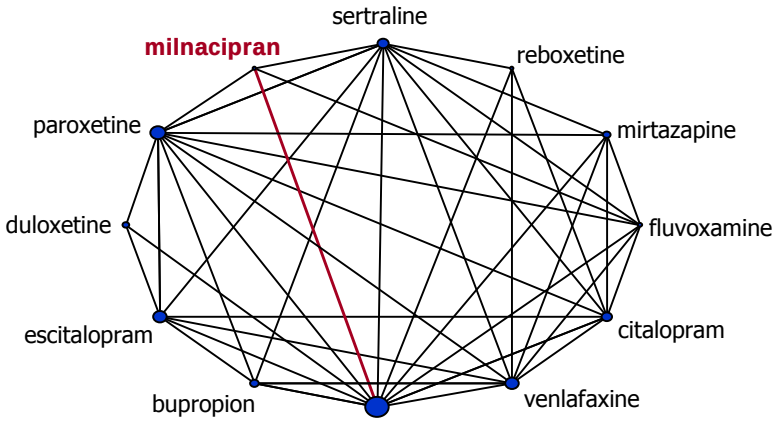


Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP: ***Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis.*** *Lancet Oncol 2007,* ***8:*** *898-911.*

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*

Why use Bayesian statistics for meta-analysis?

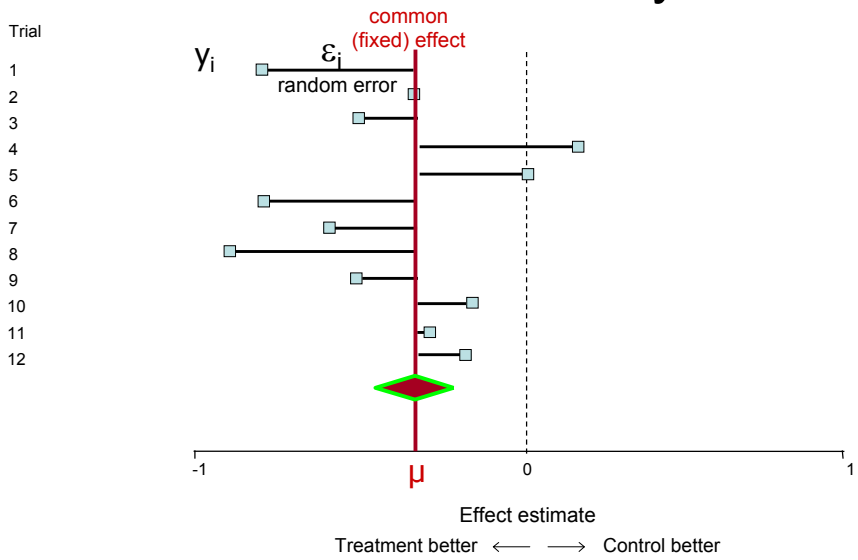
- **Natural approach for accumulating data**
- **Repeated updating of meta-analyses fine**: posterior should always reflect latest beliefs
- **People naturally think as Bayesians:** they have degrees of belief about the effects of treatment, which change when they see new data
- Probability statements about true effects of treatment easier to understand than confidence intervals and *p* -values

Why use Bayesian statistics for MTM?

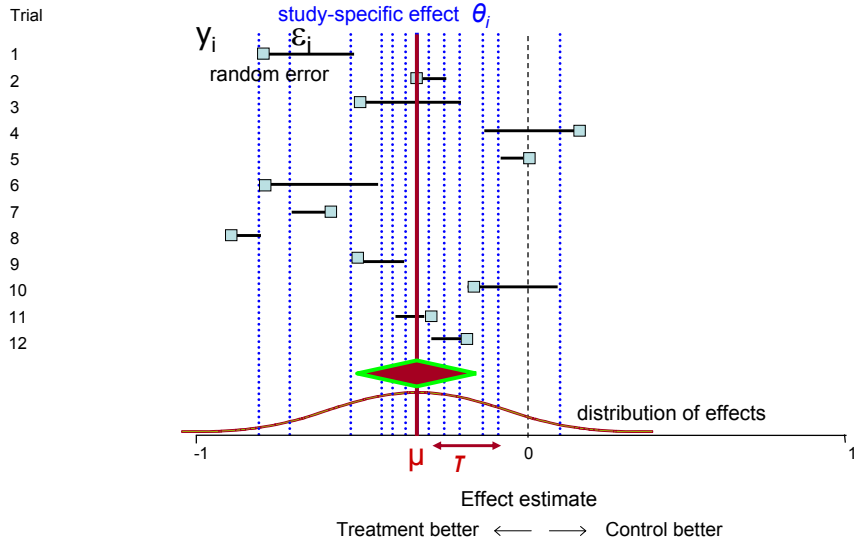
- Bayesian approach is **easier to account for correlations** induced by multi-arm trials
- Estimation of **predictive intervals** is straightforward
- Estimation of **ranking probabilities** is straightforward

- MTM with two-arm trials only (or ignoring the correlations)
  Easy with frequentist meta-regression

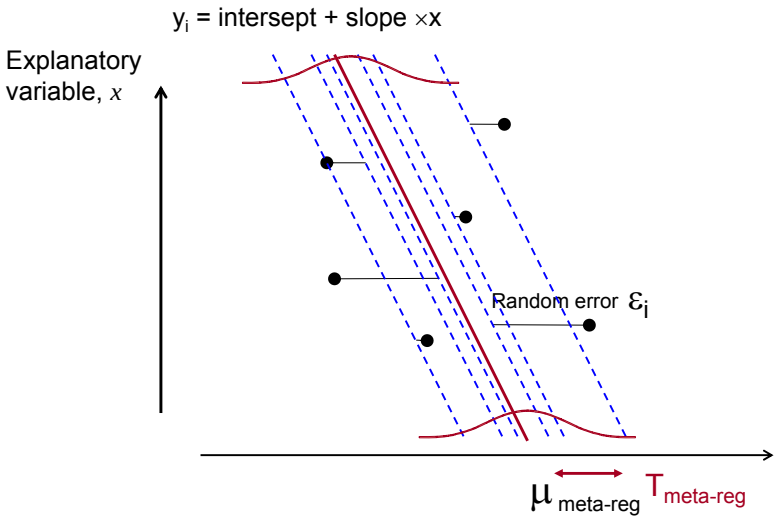
Fixed effect meta-analysis



Random effects meta-analysis



Random effects meta-regression



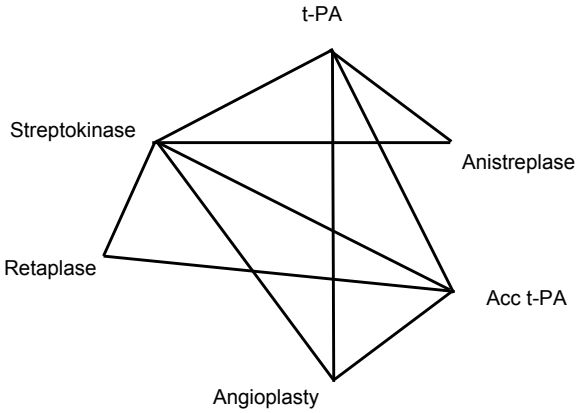
Meta-regression

- We observe y_i in each study (e.g. the log(OR))
- Meta-regression using the treatments as 'covariates'
- AC, AB, BC studies, chose C as *reference*

$$y_i = \mu^{AC} \times (Treat_i=A) + \mu^{BC} \times (Treat_i=B)$$

- The AC studies have (1,0), the BC studies (0,1) [*basic*]
- AB studies have (1,-1) [*functional*]

Parametrisation of the network



Choose basic parameters

Write all other contrasts as linear functions of the basic parameters to build the design matrix

LOR for death in treatments for MI

LOR for death in treatments for MI

$$y_i = \mu^A \text{ t-PA} + \mu^B \text{ Anistreplase}_i + \mu^C \text{ Accelerated t-PA}_i + \mu^D \text{ Angioplasty}_i + \mu^E \text{ Reteplase}_i$$

Use as 'covariates'

No. studies	Streptokinase	t-PA	Anistreplase	Acc t-PA	Angioplasty	Reteplase
3	-1	1	0	0	0	0
1	1	0	1	0	0	0
1	0	0	0	1	0	0
3	0	0	0	0	1	0
1	0	0	0	0	0	1
1		-1	1	0	0	0
2		-1	0	0	1	0
2		0	0	-1	1	0
2		0	0	-1	0	1

Lumley 2002, Stat Med

LOR for death in treatments for MI

$y_i = \mu^A$ t-PA + μ^B Anistreplase$_i$ + μ^C Accelerated t-PA$_i$ + μ^D Angioplasty$_i$ + μ^E Reteplase$_i$

$$Y = (\mu^A, \mu^B, \mu^C, \mu^D, \mu^E) \times X + \Delta$$

Matrix of all observations

Vector of LogOR

Design matrix

Random effects matrix

$$Y \sim N(\boldsymbol{\mu} X, V) \qquad \Delta \sim N(\mathbf{0}, diag(\tau^2))$$

Variance-covariance matrix (for the observed LOR)

LOR compared to Streptokinase (RE model)

$$Y = (\mu^A, \mu^B, \mu^C, \mu^D, \mu^E) \times X + \Delta$$

Treatment	LOR (SE)	OR	95% CI
t-PA	-0.02 (0.03)	0.98	(0.92, 1.04)
Anistreplase	-0.00 (0.03)	1.00	(0.94, 1.06)
Accelerated t-PA	- 0.15 (0.05)	0.86	(0.78, 0.95)
Angioplasty	- 0.43 (0.20)	0.65	(0.44, 0.96)
Reteplase	- 0.11 (0.06)	0.90	(0.80, 1.01)

What's the problem with multi-arm trials?

- We need to take into account the correlations between the estimates that come from the same study
- A B C

  y_i^{BC}

  y_i^{AC}

- The random effects (θ_i^{BC}, θ_i^{AC}) that refer to the same trial are correlated as well
- You have to built in *the correlation matrix for the observed effects*, **and** *the correlation matrix for the random effects*

$$Y \sim N(\boldsymbol{\mu} X, V) \qquad \Delta \sim N(\mathbf{0}, diag(\tau^2))$$

Hypothetical example

Study	No. arms	#	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=2	1	$y_{3,1}$, $v_{3,1}$	BC
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

Basic parameters: AB and AC

Study	No. arms	#	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=2	1	$y_{3,1}$, $v_{3,1}$	BC
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

Meta-regression

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Study	No. arms	#	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=2	1	$y_{3,1}$, $v_{3,1}$	BC
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

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Take into account correlation in observations

$$\begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} v_{1,1} & 0 & 0 & 0 & 0 \\ 0 & v_{2,1} & 0 & 0 & 0 \\ 0 & 0 & v_{3,1} & 0 & 0 \\ 0 & 0 & 0 & v_{4,1} & \mathrm{cov}\left(y_{4,1}, y_{4,2}\right) \\ 0 & 0 & 0 & \mathrm{cov}\left(y_{4,1}, y_{4,2}\right) & v_{4,2} \end{pmatrix} \right)$$

Study	No. arms	#	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=2	1	$y_{3,1}$, $v_{3,1}$	BC
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

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Take into account correlation in random effects

$$\begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau^2_{AB} & 0 & 0 & 0 & 0 \\ 0 & \tau^2_{AC} & 0 & 0 & 0 \\ 0 & 0 & \tau^2_{BC} & 0 & 0 \\ 0 & 0 & 0 & \tau^2_{AB} & \mathrm{cov}\left(\beta_{4,1}, \beta_{4,2}\right) \\ 0 & 0 & 0 & \mathrm{cov}\left(\beta_{4,1}, \beta_{4,2}\right) & \tau^2_{AC} \end{pmatrix} \right)$$

How to fit such a model?

- MLwiN
- SAS, R
- STATA using metan

Ranking measures from MTM

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

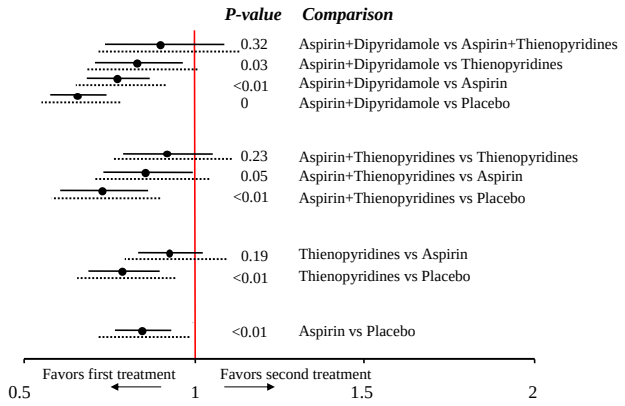
Efficacy (response rate) (95% CI) | Comparison | Acceptability (dropout rate) (95% CI)

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



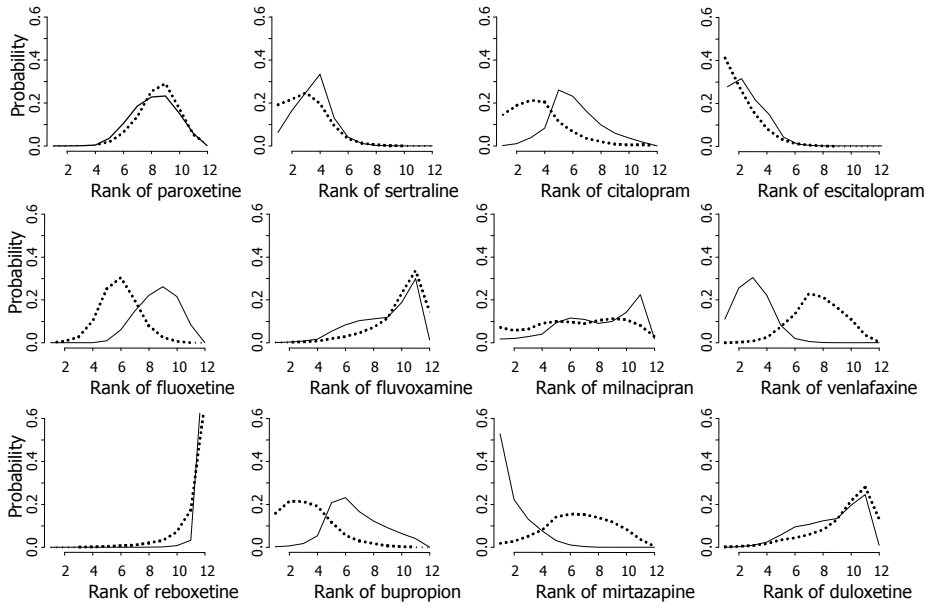
Odds Ratio for serious vascular event

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
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

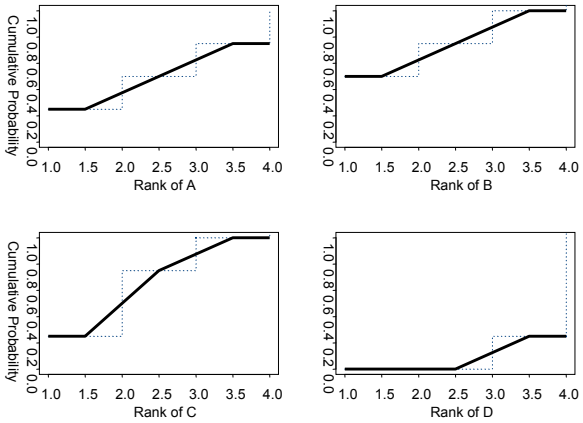
i the treatment
j the rank



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

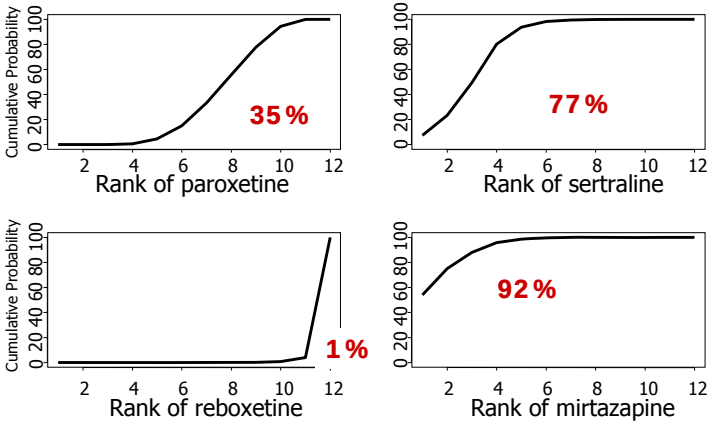
i the treatment
j the rank



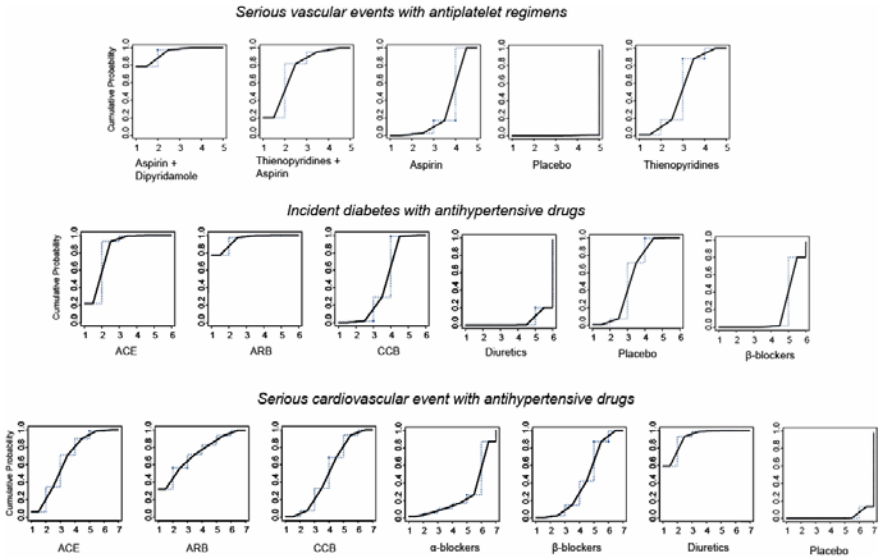
The areas under the cumulative curves for the four treatments of the example above are
A=0.5
B=0.75
C=0.67
D=0.08

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!

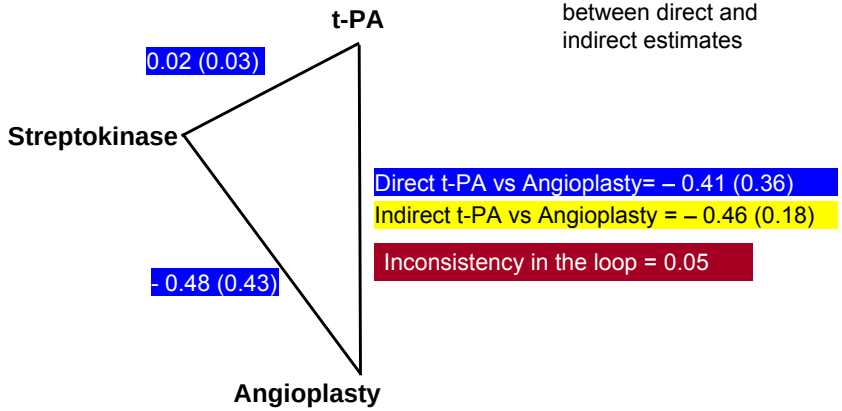


Inconsistency

- What is inconsistency?
- How it manifests itself?

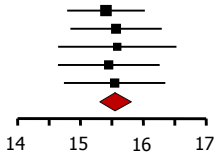
Inconsistency

LOR (SE) for MI

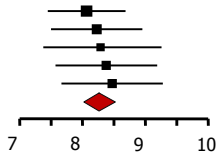


Inconsistency - Heterogeneity

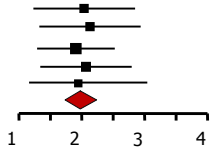
- *Heterogeneity:* 'excessive' discrepancy among study-specific effects
- *Inconsistency:* it is the excessive discrepancy among source-specific effects (direct and indirect)



AC=15.5



BC=8.2



AB=2.3

Inconsistency

Empirical Evidence

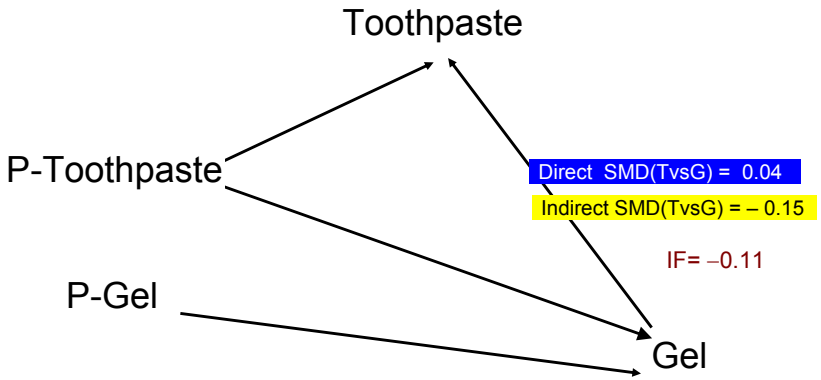
- In 3 cases out of 44 there was an important discrepancy between direct/indirect effect.
- Direction of the discrepancy is inconsistent

Glenny et al HTA 2005

What can cause inconsistency?

Inappropriate common comparator

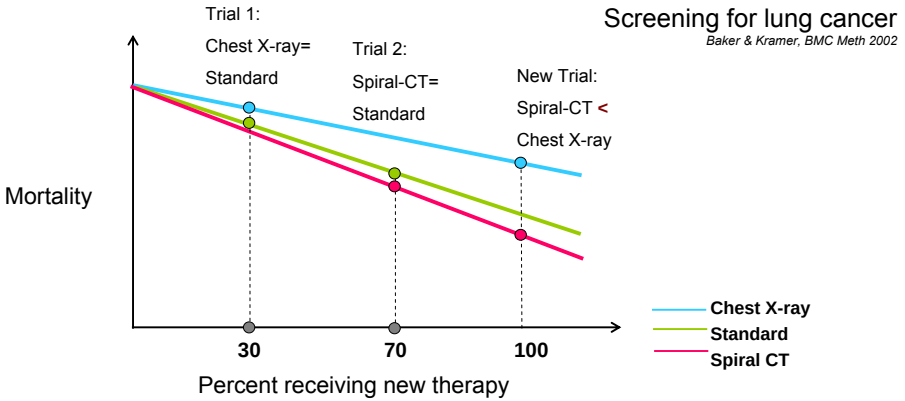
Compare Fluoride treatments in preventing dental caries



I cannot learn about Toothpaste versus Gel through Placebo!

What can cause inconsistency?

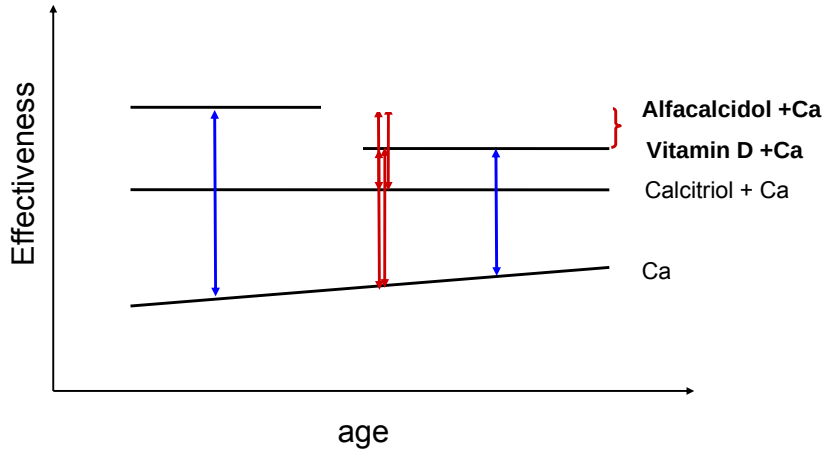
Confounding by trial characteristics



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!

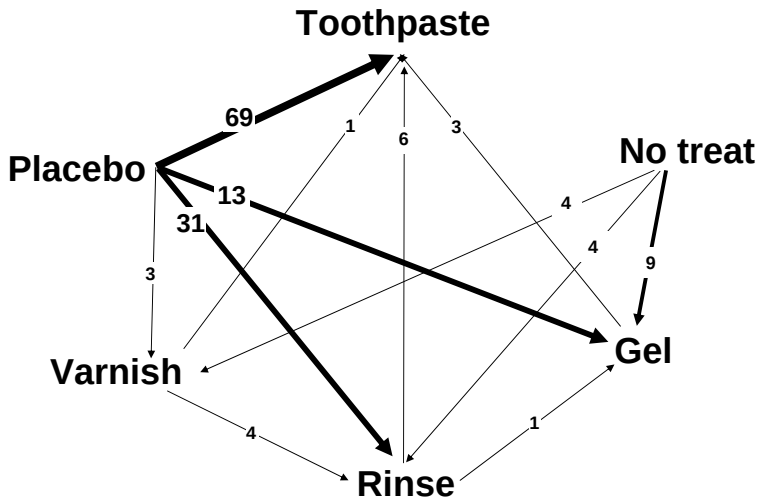
No. studies	T	G	R	V	P	Fup	Baseline	Year	Water F (yes/no)
69	■				■	2.6	11.8	1968	0.2
13		■			■	2.3	3.8	1973	0.2
30			■		■	2.4	5.9	1973	0.1
3				■	■	2.3	2.7	1983	0
3	■	■				2.7	NA	1968	0.66
6	■		■			2.8	14.7	1969	0
1	■			■		2	0.9	1978	0
1		■	■			1	NA	1977	0
1		■		■		3	7.4	1991	NA
4			■	■		2.5	7.6	1981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

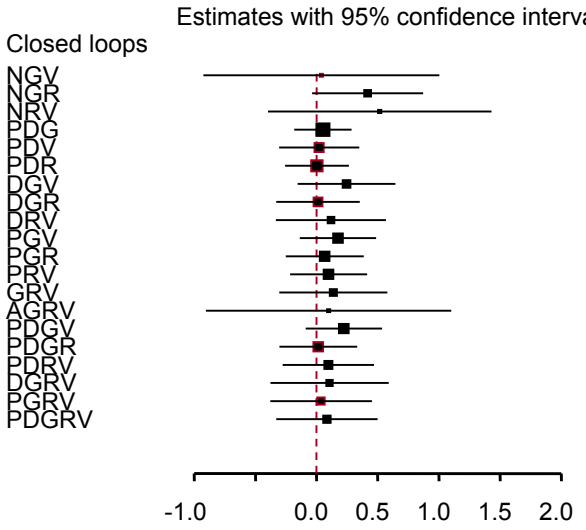
Inconsistency

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



Evaluation of concordance within closed loops



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

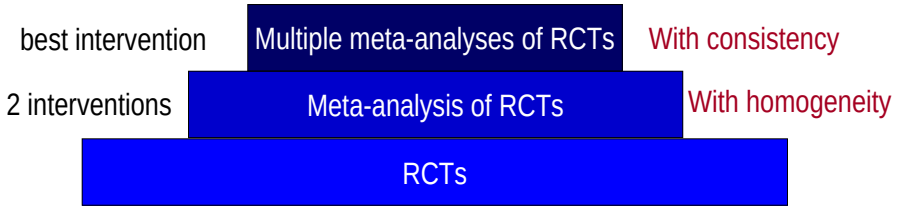
Salanti G, Marinho V, Higgins JP: **A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered.** *J Clin Epidemiol* 2009, **62:** 857-864.

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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