

Network Meta-Analysis

an introduction and example

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Introduction

Network meta-analysis

- Is an extension of normal meta-analysis
- Allows comparison of ≥ 2 alternatives
 - Integrating direct and indirect evidence
 - While checking for (in-)consistencies
- A.K.A.: Mixed/Multiple Treatment Comparison (MTC)

Introduction: meta-analysis

Study, Year (Reference)

Bennie et al., 1995 (33)*

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144

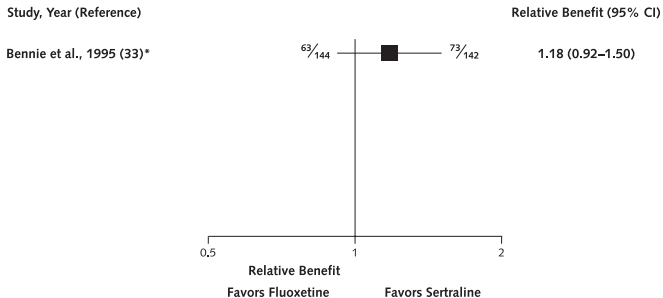
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Fluoxetine

Sertraline

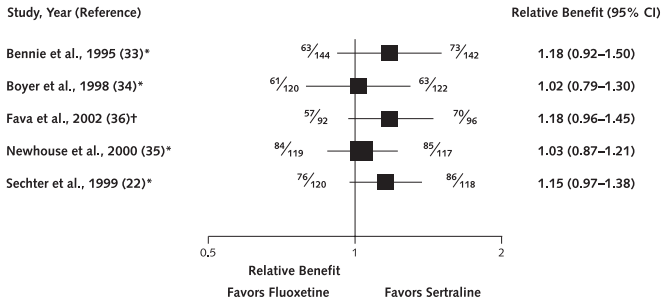
Hansen et al. Ann Intern Med 2005;143:415-426

Introduction: meta-analysis



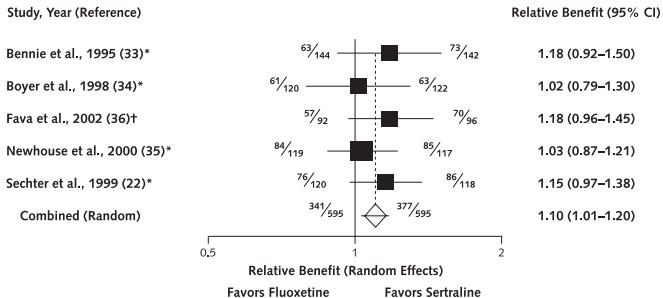
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Introduction: meta-analysis



Hansen et al. Ann Intern Med 2005;143:415-426

Introduction: meta-analysis



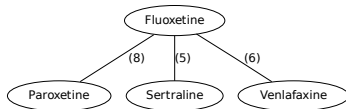
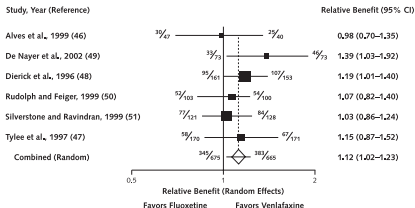
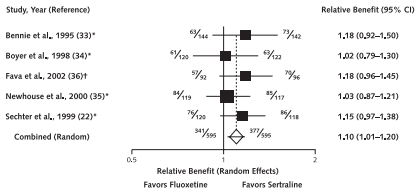
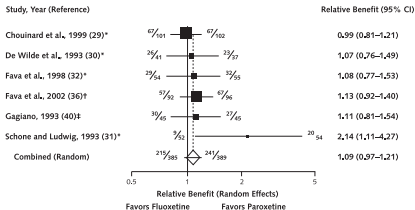
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Introduction: meta-analysis limits (1)

Hansen et al. (2005) systematic review:

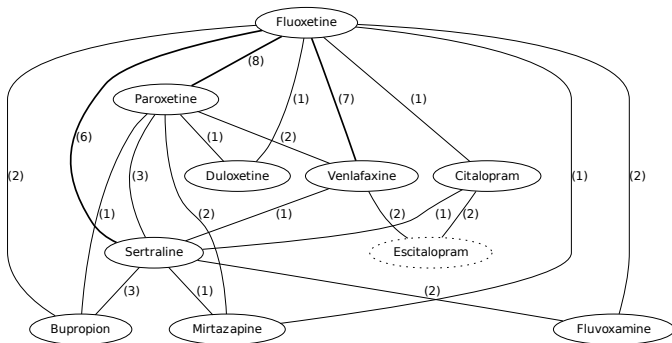
- 46 studies comparing $n = 10$ second-generation AD
- In total, 20 comparisons are available
- Out of $\frac{n(n-1)}{2} = 45$ possible comparisons
- 3 meta-analyses are performed

Introduction: meta-analysis limits (2)



Hansen et al. Ann Intern Med 2005;143:415-426

Introduction: meta-analysis limits (2)



Introduction: non-solution

Assess efficacy using a baseline (fluoxetine)...

Fluoxetine 1.00 (1.00 - 1.00)

Paroxetine 1.09 (0.97 - 1.21)

Sertraline 1.10 (1.01 - 1.20)

Venlafaxine 1.12 (1.02 - 1.23)

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- How likely is it that Venlafaxine has the greatest efficacy?

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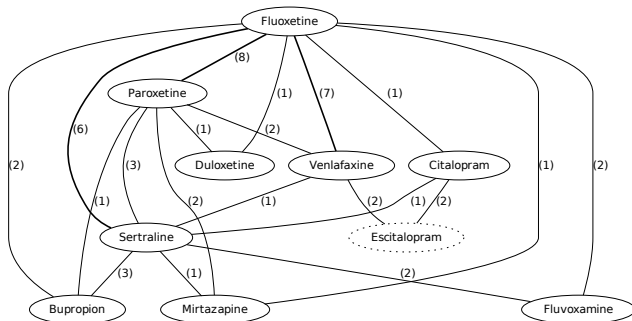
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- How likely is it that Venlafaxine has the greatest efficacy?
- What happens if we choose another baseline?
 - Other studies included → possibly different results
- Not all drugs can be included (escitalopram)
- We're "double counting" multi-arm trials

Introduction: network meta-analysis



Include **all** evidence in one analysis

Network Meta-Analysis models

- We will construct a Bayesian hierarchical model
- We can use MCMC software (BUGS, JAGS) to estimate it

Network Meta-Analysis models

- We will construct a Bayesian hierarchical model
- We can use MCMC software (BUGS, JAGS) to estimate it
- Our software (<http://drugis.org/>) can do it for you

Level 1 (likelihood)

- Modeling the effect r_{ik}/n_{ik} ,
- for treatment k of study i ,
- as a binomial process with success probability p_{ik} :

$$r_{ik} \sim \text{Bin}(p_{ik}, n_{ik})$$

Using MCMC simulation, the model converges to maximum joint likelihood estimate of these p_{ik} given the data on r_{ik} and n_{ik} .

Linkage

Apply a transformation to obtain normally distributed variable:

$$\theta_{ik} = \text{logit}(p_{ik}) = \log \frac{p_{ik}}{1 - p_{ik}} ; p_{ik} = \text{logit}^{-1}(\theta_{ik})$$

And choose a baseline $b(i)$ and define θ_{ik} (the log odds) in terms of a baseline μ_i and relative effect $\delta_{ib(i)k}$ (the log odds-ratio):

$$\theta_{ik} = \mu_i + \delta_{ib(i)k}$$

Level 2 (random effects)

We assume the relative effects (LORs) to be normally distributed:

$$\delta_{ixy} = \mathcal{N}(d_{xy}, \sigma_{xy}^2)$$

And, for a three-arm trial i with treatments x, y, z , $b(i) = x$:

$$\begin{pmatrix} \delta_{ixy} \\ \delta_{ixz} \end{pmatrix} \sim \mathcal{N} \left(\begin{pmatrix} d_{xy} \\ d_{xz} \end{pmatrix}, \begin{pmatrix} \sigma_{xy}^2 & \rho_{xy,xz} \sigma_{xy} \sigma_{xz} \\ \rho_{xy,xz} \sigma_{xy} \sigma_{xz} & \sigma_{xz}^2 \end{pmatrix} \right)$$

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Under the assumption of equal variances

Level 3 (Priors)

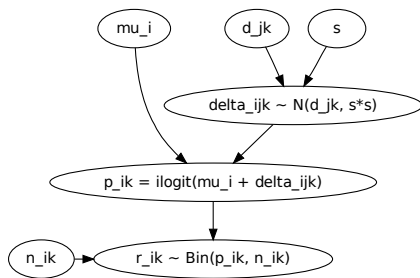
For each of the parameters of interest, μ_i , d_{jk} and σ , specify priors:

$$\mu_i \sim \mathcal{N}(0, 1000)$$

$$d_{jk} \sim \mathcal{N}(0, 1000)$$

$$\sigma \sim U(0, 2)$$

Overview



So far, this is just a random effects meta-analysis!

Consistency assumption

Assuming consistency:

$$d_{yz} = d_{xy} - d_{xz}$$

- 'Borrow strength' from indirect evidence.
- The left-hand term (d_{yz}) is a *functional parameter*
- The right-hand terms (d_{xy}, d_{xz}) are *basic parameters*
- Only basic parameters are stochastic

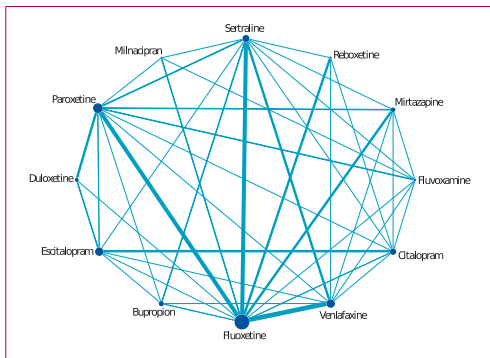
Inconsistency Factors

Introduce an 'inconsistency factor' for each functional parameter:

$$d_{yz} = d_{xy} - d_{xz} + w_{xyz}$$

- After the model has converged, we test $w_{xyz} = 0$
- Comparing inconsistency and consistency models on model fit also useful
- Correctly specifying the model is tricky

Example: evidence network



Cipriani et al. Lancet 2009;373:746-758

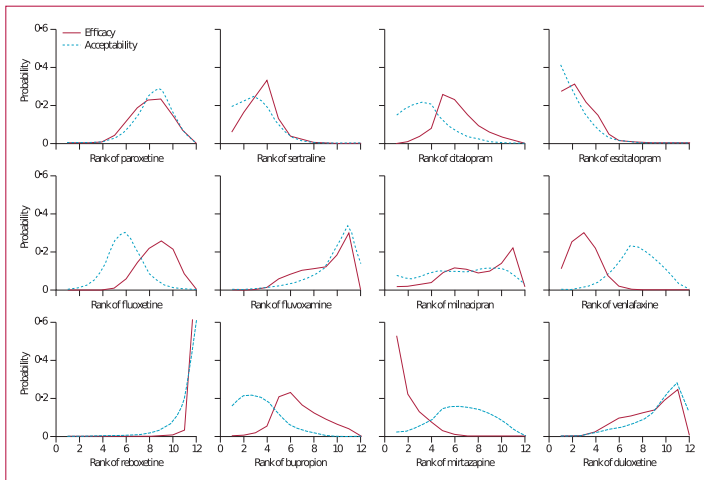
Example: results (LOR)

■ 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)	QT	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 (1.09-1.88)	1.19 (0.91-1.57)	0.98 (0.67-1.41)	1.16 (0.72-1.73)	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 (1.02-1.55)	FLU	0.82 (0.62-1.07)	0.97 (0.69-1.32)	0.97 (0.72-1.21)	0.91 (0.79-1.05)	0.70 (0.63-0.92)	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 (0.78-1.38)	1.35 (1.03-1.76)	1.02 (0.81-1.30)	FAK	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 (1.09-2.08)	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)	VBN

Cipriani et al. Lancet 2009;373:746-758

Example: results (rank probabilities)



Example: MTC in ADDIS (<http://drugis.org/addis>)

Our software:

- Aggregate Data Drug Information System (ADDIS) v0.8
- Open-source (freely available) software
- (XML) Database of clinical trial results
- Meta-analysis and network meta-analysis
- See <http://drugis.org/>

Example: MTC in ADDIS (<http://drugis.org/addis>)

Overview

1. Select Indication
2. Select Endpoint
3. Select Drugs
4. Select Studies
5. Select Arms
6. Overview

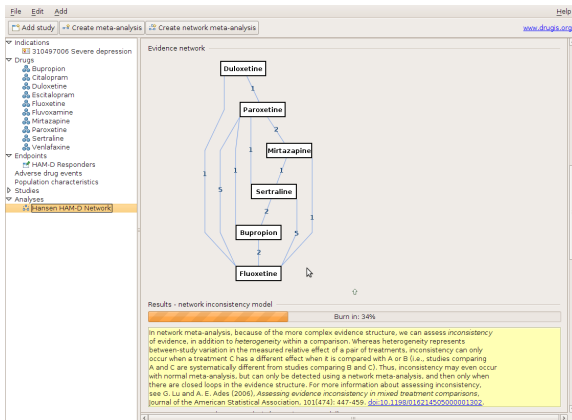
Select Drugs

Select the drugs to be used for the network meta-analysis. To continue, (1) at least two drugs must be selected, and (2) all selected drugs must be connected.

Network diagram showing connections between various antidepressant drugs. Selected drugs are highlighted in green: Bupropion, Duloxetine, Fluoxetine, Mirtazapine, Sertraline, and Venlafaxine. Other drugs shown in grey boxes include Fluvoxami..., Citalopram, Paroxetine, and Escitalopr... The network is a complex graph with nodes representing drugs and edges representing connections, with numerical weights on the edges.

◀ Previous Next ▶ Last Finish Cancel

Example: MTC in ADDIS (<http://drugis.org/addis>)



Example: MTC in ADDIS (<http://drugis.org/addis>)

File Edit Add Help

Add study → Create meta-analysis → Create network meta-analysis www.drugis.org

310497006 Severe depression

Drugs

- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Mirtazapine
- Paroxetine
- Sertraline
- Venlafaxine

Endpoints

- HAM-D Responders
- Adverse drug events
- Population characteristics

Studies

- Hansen HAM-D Network
- Hansen HAM-D Small

Results - network inconsistency model

In network meta-analysis, because of the more complex evidence structure, we can assess inconsistency of evidence, in addition to heterogeneity within a comparison. Whereas heterogeneity represents between-study variation in the measured relative effect of a pair of treatments, inconsistency can only occur when a treatment C has a different effect when it is compared with A or B (i.e., studies comparing A and C are systematically different from studies comparing B and C). Thus, inconsistency may even occur with normal meta-analysis, but can only be detected using a network meta-analysis, and then only when there are closed loops in the evidence structure. For more information about assessing inconsistency, see G. Lu and A. E. Ades (2006), Assessing evidence inconsistency in mixed treatment comparisons, *Journal of the American Statistical Association*, 101[474]: 447-459. doi:10.1198/016214505000011302.

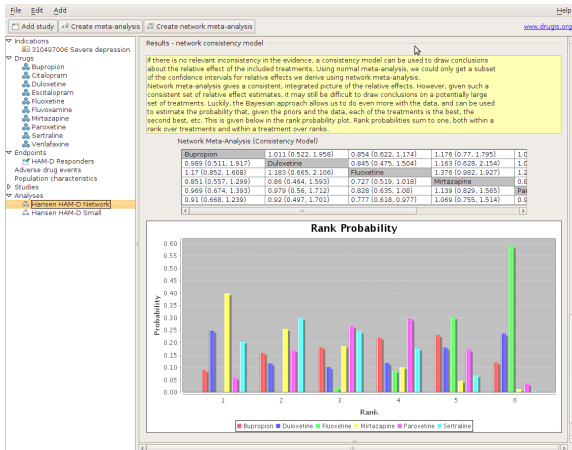
Network Meta-Analysis (Inconsistency Model)

Bupropion	1.138 (0.559, 2.305)	0.938 (0.657, 1.338)	1.305 (0.773, 2.205)	1.1
0.881 (0.434, 1.788)	Duloxetine	0.792 (0.425, 1.478)	1.15 (0.563, 2.347)	1.0
1.056 (0.747, 1.521)	1.262 (0.677, 2.355)	Fluoxetine	1.392 (0.933, 2.076)	1.2
0.766 (0.453, 1.294)	0.87 (0.426, 1.776)	0.718 (0.482, 1.072)	Mirtazapine	0.8
0.842 (0.479, 1.479)	0.984 (0.543, 1.782)	0.812 (0.61, 1.082)	1.215 (0.868, 1.701)	0.9
0.949 (0.647, 1.392)	0.956 (0.494, 1.851)	0.79 (0.623, 1.002)	1.046 (0.688, 1.59)	0.8

Inconsistency Factors

Cycle	Confidence Interval
Bupropion, Paroxetine, Fluoxetine	0.028 (-0.411, 0.408)
Bupropion, Sertraline, Fluoxetine	-0.119 (-0.511, 0.273)
Fluoxetine, Paroxetine, Duloxetine	-0.042 (-0.515, 0.432)
Fluoxetine, Mirtazapine, Paroxetine	-0.072 (-0.463, 0.319)
Fluoxetine, Mirtazapine, Sertraline	0.09 (-0.371, 0.471)
Fluoxetine, Paroxetine, Sertraline	0.095 (-0.293, 0.484)

Example: MTC in ADDIS (<http://drugis.org/addis>)



Our research (<http://drugis.org/>)

- MTC model generation
- Multi-criteria benefit-risk analysis based on MTC
- Application of MTC-BR to Hansen et al. (2005)
 - With Jing Zhao (for her MSc thesis)
- Decision support for drug regulation
- Software for all of the above

Discussion

Should network meta-analysis be used?

- Can it be avoided?
- No real alternative for multi-treatment analysis.
- Improved transparency
 - No need to lump treatments
 - No arbitrary exclusion of evidence (through baseline choice)
- Same assumptions as meta-analysis

Discussion

Disadvantages Bayesian (MCMC) approach:

- Model specification difficult
- Choosing good priors
- Assessing convergence + run length
- Sensitivity to different 'equivalent' parametrizations?