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The role of MTM in Overviews of Reviews

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Comparing Multiple Interventions Methods Group

Keystone, 2010

Why we need overviews of reviews

- Explosion in RCTs necessitated systematic reviews.
- More recently an explosion in systematic reviews
  - Over 3000 published reviews on Cochrane library
  - Multiple reviews for same clinical condition
  - 22 reviews of smoking cessation interventions (42 distinct regimes in 38 separate meta-analyses)
  - Management of adult asthma (19 reviews)
  - Management of primary hypertension (9 reviews, 10 protocols).

Aim of an overview of reviews

- Originally formulated to:
  - Summarise results of multiple reviews into a single accessible document.
  - Don’t repeat/ update literature searches, eligibility assessment or evidence synthesis
    - Extract summary effect estimates as reported in component reviews, reformatted in tables or figures
- Audience: decision makers/ clinicians
  - “Which treatment should I use for this condition?”

Example: nocturnal enuresis*

Treatment comparison	RR	95% CI	% change
Alarm vs no treatment	0.38	0.33 – 0.45	62%
Alarm vs DBT	1.33	0.79 – 2.24	-13%
Alarm vs Desmopressin	0.71	0.50 – 0.99	12%
Alarm vs Imipramine	0.73	0.61 – 0.88	22%
Alarm vs CBT	0.68	0.52 – 0.90	29%
CBT vs no treatment	0.69	0.55 – 0.85	31%
DBT vs no treatment	0.82	0.66 – 1.02	16%
DBT + alarm vs no treatment	0.17	0.11 – 0.28	83%
Diclofenac vs no treatment	0.52	0.38 – 0.70	43%
Imipramine vs no treatment	0.77	0.72 – 0.83	20%

OUTCOME: Failure to achieve 14 days consecutive dry nights

*Russell & Kiddoo (2006) *Evid-Based Child Health*

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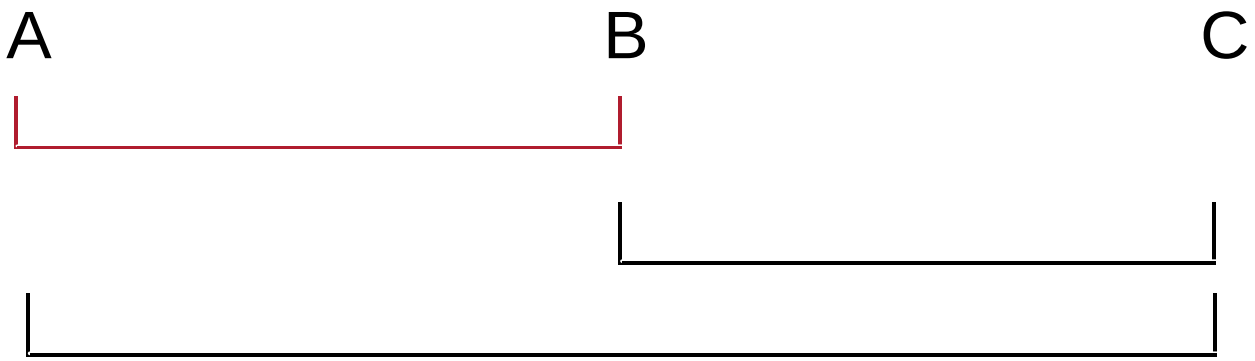
Indirect comparisons

- In absence of direct evidence for treatments B vs C, an *indirect* estimate of log risk ratio lrr_{BC} can be obtained from RCTs comparing A vs B and A vs C:



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

*Bucher HC, et al.(1997); Glenny et al (2005)

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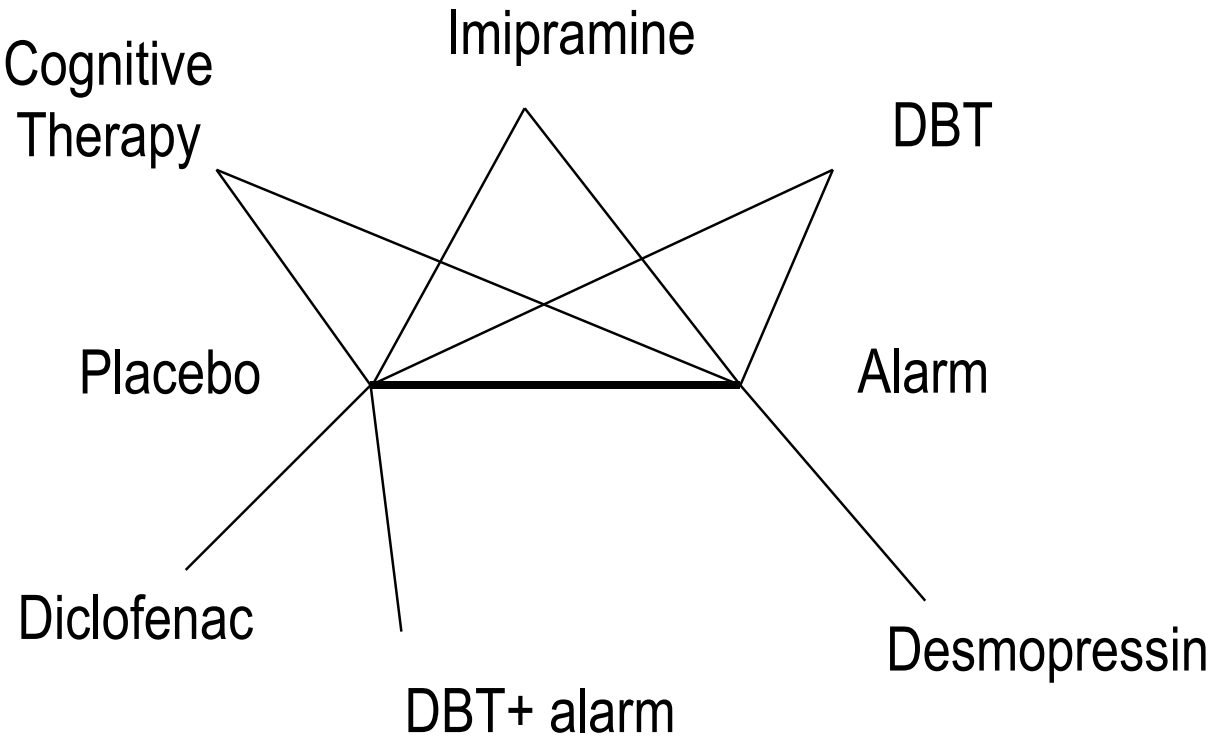
Multiple treatment meta-analysis

- Simultaneous comparison of multiple treatments
  - Internally consistent set of estimates of relative treatment effect
  - Probability that each treatment is the most effective
- Key assumption: $\hat{d}_{BC} = \hat{d}_{AC} - \hat{d}_{AB}$
  - The $\hat{d}_{BC}$ estimated in the BC trials is the same as the $\hat{d}_{BC} = \hat{d}_{AC} - \hat{d}_{AB}$ estimated in the AC and AB trials.
- Concern that assumption of *consistency* is not 'safe'.

Network of evidence



Fixed effect summaries

Treatment comparison	RR (reported)	RR (MTC)	Deviance
Alarm vs no treatment	0.38	0.46	6.4
Alarm vs DBT	1.33	0.64	7.8
Alarm vs Desmopressin	0.71	0.71	0.99
Alarm vs Imipramine	0.73	0.61	3.83
Alarm vs CBT	0.68	0.67	0.45
CBT vs no treatment	0.69	0.69	0.65
DBT vs no treatment	0.82	0.72	2.19
DBT+alarm vs no treatment	0.17	0.17	1.00
Diclofenac vs no treatment	0.52	0.52	1.01
Imipramine vs no treatment	0.77	0.75	1.47

Fixed effect summaries

Treatment comparison	RR (reported)	RR (MTC)	Deviance
Alarm vs no treatment	0.38	0.46	**6.4**
Alarm vs DBT	1.33	0.64	**7.8**
Alarm vs Desmopressin	0.71	0.71	0.99
Alarm vs Imipramine	0.73	0.61	**3.83**
Alarm vs CBT	0.68	0.67	0.45
CBT vs no treatment	0.69	0.69	0.65
DBT vs no treatment	0.82	0.72	**2.19**
DBT+alarm vs no treatment	0.17	0.17	1.00
Diclofenac vs no treatment	0.52	0.52	1.01
Imipramine vs no treatment	0.77	0.75	1.47

Residual deviance: 25.8

Reconsider the evidence……

- Inappropriate use of fixed effect summaries under-estimating uncertainty?
  - Statistically significant heterogeneity in 7/ 10 pair-wise contrasts.
- Random effects pairwise meta-analyses for each comparison in Stata.
- Random effects pooled estimates used in aggregate level MTC.

Random effects pooled summaries

Treatment comparison	RR	Expected RR	Deviance
Alarm vs control	0.38	0.40	0.778
Alarm vs DBT	0.75	2.06	0.124
Alarm vs Desmopressin	1.41	1.42	0.997
Alarm vs Imipramine	1.37	1.69	0.321
Alarm vs CBT	1.47	1.62	0.503
CBT vs control	0.69	0.66	0.555
DBT vs control	0.82	0.83	1.001
DBT + alarm vs control	0.17	0.19	0.994
Diclofenac vs control	0.52	0.52	0.995
Imipramine vs control	0.77	0.68	0.848

Residual deviance = 7.113

Probability treatment *x* is 'best':

Random effects		
	14 day dry nights	**Probability best**
Nothing	0.93	0%
Alarm	0.38	12.4%
DBT	0.78	0.0%
Desmopressin	0.55	0.3%
Imipramine	0.64	0.0%
CBT	0.6	1.1%
DBT+alarm	**0.23**	**84.8%**
Diclofenac	0.49	1.4%

Summary

- MTM the only way to generate coherent summaries of treatment effect in OoRs.
- I used a pooled summaries MTM here for teaching purposes only
- Trial-level MTM is preferable because:
  - Pooled summaries are further level of aggregation: more susceptible to confounders? (ecological fallacy)
  - Summaries from component reviews subject to approximations (e.g. continuity corrections)
  - Multi-arm trials handled correctly
  - More detail on this will be provided in the basic and advanced MTM sessions (on Thursday and Friday – see programme book for more detail).

Comparing Multiple Interventions Methods Group

- Recently formed (registered on 27th Sept!) to address the issues we have outlined in this workshop.
- The scope of the group will focus on methodology for comparing multiple interventions for a common condition, both in Cochrane Intervention reviews addressing multiple interventions and in Cochrane Overviews of reviews.
- We also aim to provide peer review and specialist advice to review teams and CRGs.
- Co-convenors are:
  - Lorne Becker (USA), Deborah Caldwell (UK), Julian Higgins, (UK)Tianjing Li (USA), Georgia Salanti (Greece) and Chris Schmidt (USA).