Comparing Multiple Treatments:  
Overviews vs. Intervention Reviews

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Essential Features

• Addresses a well-defined question
• Compares 2 or more interventions
• Search strategy uses existing reviews
• Provides a synthesis or integration across existing reviews

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A Well-Defined Question

• PICO – Population, Interventions
• "Would it be reasonable to compare these interventions in different arms of a single RCT?"
  – Important assumption for some statistical analyses
  – Useful rule of thumb for all overviews
Interventions for Bronchiolitis

- Placebo
- Salbutamol
- Steroid
- Epinephrine
- No Treatment
- Chest Physiotherapy
- Nebulized 3% saline
- Nebulized 0.9% saline
- Nebulized 1.3% saline
- Heliox Inhalation
- Antibiotic
- Oxygen Inhalation

Compares 2 or More Interventions

- Overviews are one way of doing this
- Many Cochrane intervention reviews do this as well
- What are the differences?
- How to choose whether to use an overview or an intervention review to compare multiple interventions

Intervention Review or Overview?

- No firm guidelines
- May depend on the question
- May depend on the available evidence
- We will explore some differences & some options for both approaches
Differences Between Overviews and Intervention Reviews

- **Search Strategy** – Always differs
  - Intervention reviews search for trials
  - Overviews search for reviews
- **Approach to Analysis** – Sometimes differs
  - Intervention reviews use a trial level analysis
  - Overviews may be able to use a review level analysis
    - But will often use a trial level analysis instead

Search Strategy for Overviews

- **Focus on identifying relevant reviews**
  - Use reviews to find relevant trials if trial level analysis is contemplated
- **Extending the search**
  - Some overviews use non-Cochrane reviews
  - Updating search for older reviews
  - Trial level search for interventions not included in reviews

Synthesis or Integration

- **Driven by the well-defined question**
- **Not driven by the individual review questions**
- **Outcomes part of PICO**
  - Specified in overview protocol
  - Depends in part on choices made by trialists or reviewers
  - May force a trial level analysis
12 new generation antidepressants: Which ones are the most efficacious?

Example of a trial level synthesis

With thanks to Georgia Salanti

Network of Randomized trials

No trials comparing reboxetine to bupropion?
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Network of Randomized Trials

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

Three indirect comparisons of reboxetine to bupropion

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12 new generation antidepressants:

Most effective
Mirtazapine
Escitalopram
Venlafaxine
Sertraline
Milnacipran
Bupropion
Citalopram
Fluoxetine
Paroxetine
Duloxetine
Fluvoxamine
Reboxetine

Least effective

Ranking according to the efficacy

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Defining treatments: are all relevant treatments included?

• Definition of relevance depends on your research question and analysis plan
  – Which is the best antidepressant?
  – Rankings may be affected by inclusion criteria.
  – Consider including placebos, TAU, older and legacy treatments
  – Do NG antidepressants improve outcome?
  – An “in principle” question.
• Requires early collaboration with clinicians, epidemiologists etc.
Defining treatments: lumping or splitting

'Lumping' in meta-analysis is commonplace as it only allows 2 treatments to be compared.

- **1. CBT vs TAU:** RR 2.00 (1.55, 2.58)
- **2. Humanistic vs TAU:** RR 0.60 (0.26, 1.40)
- **3. Mindfulness vs TAU:** RR 1.50 (0.77, 2.93)
- **Psychotherapy vs TAU:** RR 1.73 (1.38, 2.17)

"Lumped" psychotherapy versus treatment as usual forest plot

Meta-analysis: to lump, or to split...

Lumping treatments: Can mask heterogeneity, increased power, increase precision (spuriously?).

- **E.g. PTCA vs thrombolytics**
  - PTCA better than thrombolytics (OR 0.70 [0.58 – 0.85])

  Subsequent correspondence:
  - "But surely the relevant comparison is the 'best' thrombolytic (Act t-PA) NOT the 'average' one?"
  - PTCA vs Act t-PA not "significant" (OR 0.81 [0.62 – 1.02])
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**Network meta-analysis: to lump or to split...**

Trials of HAART regimes for HIV

A: 2 NRTIs
B: 2 NRTIs + PI
C: 2 NRTIs + NNRTI

"Indirect B vs C evidence inconsistent with direct evidence from B vs C trials"

"Indirect Comparisons unreliable for complex interventions like HAART"

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**Network meta-analysis: to lump or to split...**

A: 2 NRTIs , B: 2 NRTIs + PI, C: 2 NRTIs + NNRTI

BUT the NRTIs in the A vs B trials were DIFFERENT from the NRTIs in the B vs C trials.

When the comparison was restricted to trials with the SAME NRTI regimes, the inconsistency no longer statistically ‘significant’.

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**Review Level Analysis**

**Interventions for Enuresis**

- Placebo
- Alarm
- Cognitive Therapy
- Imipramine
- Dry bed training
- Desmopressin
- Diclofenac
  - Dry bed training + Alarm

*J Clin Epidemiol. 63:875-82 PMID: 20080027*
Trial or Review summaries for NMA?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prob best</th>
<th>RR (no treatment)</th>
<th>RR (no treatment)</th>
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<td>0</td>
<td>0</td>
<td>0.90 (0.80, 1.05)</td>
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<tr>
<td>Del</td>
<td>0.81</td>
<td>0.82 (0.64, 1.05)</td>
<td>0.87 (0.69, 1.12)</td>
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<td>Desmopressin</td>
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<td>0.50 (0.33, 0.82)</td>
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<td>Imipramine</td>
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<td>0.59 (0.36, 0.95)</td>
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<td>Diclofenac</td>
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<td>0.68 (0.50, 0.94)</td>
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<td>DBT + alarm</td>
<td>0.78</td>
<td>0.19 (0.05, 0.76)</td>
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<tr>
<td>DBT</td>
<td>0.13</td>
<td>0.46 (0.16, 1.38)</td>
<td>0.12 (0.16, 1.35)</td>
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Example of a Synthesis

An overview of reviews evaluating the effects of financial incentives in changing healthcare professional behaviours and patient outcomes

DOI: 10.1002/14651858.CD008608.

Reviews included
- 2 Cochrane reviews
- 2 non-Cochrane reviews
Stated Aims of the Reviews

- To estimate the effectiveness and efficiency of interventions to change outpatient referral rates or improve outpatient referral appropriateness.
- To review the impact of payment systems on the behaviour of primary care physicians.
- To assess the relationship between explicit financial incentives and the provision of high-quality health care by systematically reviewing empirical studies.
- To determine the effects on drug use, healthcare utilisation, health outcomes and costs (expenditures) of (pharmaceutical) policies, that intend to affect prescribers by means of financial incentives.

A Priori Classification of Types of Incentives

- Payment for working for a specified time period (e.g. salary, sessional payment)
- Payment for each service/episode/visit (fee-for-service)
- Payment for providing care for a patient or specific population (e.g. capitation)
- Payment for providing a pre-specified level or change in activity or quality of care (e.g. includes target payments, bonuses)
- Mixed and other (comprising more than one of the above groups or not classifiable)

Outcomes From The 4 Reviews

- Consultation/Visit rates
- Processes of care
- Referrals/Admissions
- Compliance with guidelines
- Prescribing costs
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**Data on Incentive-Outcome Pairs**

**Review G**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Consultation or Visit rates</th>
<th>Processes of care</th>
<th>Referrals or Admissions</th>
<th>Compliance with guidelines</th>
<th>Prescribing costs</th>
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### Slide 29

**Data on Incentive-Outcome Pairs**

**Review A**

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<th>Consultation or Visit rates</th>
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**Data on Incentive-Outcome Pairs**

**Study Level Analysis**

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<td>Overall effect within intervention</td>
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Overviews vs. Intervention Reviews

- Overview is less resource-intensive
  - Easier search
  - Possibility of review-level analysis

**BUT**

- Depends on availability of enough good reviews
- In some cases, an intervention review may be easier

Overview as Part of a Process

- Protocol specifies the question
- Overview as the first step
  - May adequately address the question
- Intervention review if resources allow
  - Informed by overview process and results

Where to Learn More

- Comparing Multiple Interventions Methods Group
- Cochrane.org