Identifying Effective Components of Complex Interventions: Component Network Meta-Analysis (II)

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Overview

- Component Network Meta-Analysis Models
  - Common effect (“lumped” MA)
  - Additive component effects
  - Two-way interaction models
  - Full interaction models (“split” NMA)

- Illustrative examples
  - Psychological interventions for CHD
  - Electronic interventions for smoking cessation
  - CBT for depression
  - Combination therapies for COPD
Psychological Interventions for CHD
Welton et al, AJE 2009: 169: 1158-1165

• Updated Cochrane review (Rees et al. Cochrane 2004)
  • 51 studies identified

• Binary outcomes
  • Total mortality, cardiac mortality, non-fatal MI
  • Binomial likelihood and model on the log-odds ratio \( \delta_{i,k} \) in study \( i \) arm \( k \), relative to arm 1

• Continuous outcomes
  • Total cholesterol, systolic BP, diastolic BP, Depression, anxiety
  • Normal likelihood and model mean difference in \( \delta_{i,k} \)
    • … or standardised mean difference
Network Meta-Analysis Model

- Relative effect in study $i$ arm $k$ relative to arm 1
  - Fixed Effect Model:
    \[
    \delta_{i,k} = d_{Int_{i,k}} - d_{Int_{i,1}}
    \]
  - Log-odds ratio or mean difference or SMD
  - Intervention on arm $k$ of study $i$
  - Intervention on arm 1 of study $i$

- Random Effects Model:
  \[
  \delta_{i,k} \sim N \left( d_{Int_{i,k}} - d_{Int_{i,1}}, \tau^2 \right)
  \]
- $d_{Int}$ is the effect of intervention $Int$
  - relative to reference intervention
- Component models given to $d_{Int}$
- Between study variance
Interventions

- Interventions were classified as combinations of the following characteristics:
  - Usual care (USUAL)
  - Education (EDU)
  - Behavioural (BEH)
  - Cognitive (COG)
  - Relaxation (RELAX)
  - Support (SUPP)

- For example
  - EDU + COG + RELAX; EDU + BEH; etc.

- 32 possible combinations
  - 19/32 with evidence (all outcomes); 10/32 (depression)
Overview of Component NMA Models

Model M1: Single effect: interventions are "lumped" together as a single comparator

Model M2: Additive main effects: separate effect for each component within an intervention

Model M3: Two way interactions: interaction between components (synergistic / antagonistic effects)

Model M4: Full interaction: each combination of components has a different effect (i.e. "split" NMA)
Model M1: Single effect

- All psychological interventions have the same effect compared with usual care:
  \[ d_{Int} = \begin{cases} 
  0 & \text{Int} = \text{USUAL} \\
  \beta_{PSYCH} & \text{Int} \neq \text{USUAL} 
  \end{cases} \]

- Same as standard pairwise meta-analysis

- Can answer the question:
  - “Are psychological interventions, in general, effective compared with usual care?”
Model M2: Additive main effects

- The effect of each intervention is the sum of the effects of the component parts

\[ d_{\text{Int}} = \beta_{\text{EDU}} I_{\text{Int} \supset \text{EDU}} + \beta_{\text{BEH}} I_{\text{Int} \supset \text{BEH}} + \beta_{\text{COG}} I_{\text{Int} \supset \text{COG}} \]

\[ + \beta_{\text{RELAX}} I_{\text{Int} \supset \text{RELAX}} + \beta_{\text{SUPP}} I_{\text{Int} \supset \text{SUPP}} \]

\( I_{\text{Int} \supset \text{EDU}} \) is 1 if there is an EDU component in Int and 0 otherwise, etc.

- E.g. if Int=BEH+COG, then \( d_{\text{Int}} = \beta_{\text{BEH}} + \beta_{\text{COG}} \)

- Can answer the question:
  - “Are psychological intervention containing a specific component effective compared with interventions without that component (all other things being equal)?”

- Can predict effect for combinations not included in RCTs
Model M3: Two-Way Interaction Model

- Allows pairs of components to have a bigger (synergistic) or smaller (antagonistic) effect than the sum of the 2 component main effects

\[ d_{\text{Int}} = \beta_{\text{EDU}} I_{\text{Int} \supset \text{EDU}} + \beta_{\text{BEH}} I_{\text{Int} \supset \text{BEH}} + \beta_{\text{COG}} I_{\text{Int} \supset \text{COG}} \]

\[ + \beta_{\text{RELAX}} I_{\text{Int} \supset \text{RELAX}} + \beta_{\text{SUPP}} I_{\text{Int} \supset \text{SUPP}} \]

\[ + \beta_{\text{EDU,BEH}} I_{\text{Int} \supset \text{EDU}} I_{\text{Int} \supset \text{BEH}} + \beta_{\text{EDU,COG}} I_{\text{Int} \supset \text{EDU}} I_{\text{Int} \supset \text{COG}} + \ldots \]

- E.g. if \( \text{Int}=\text{BEH}+\text{COG} \), then

\[ d_{\text{Int}} = \beta_{\text{BEH}} + \beta_{\text{COG}} + \beta_{\text{BEH,COG}} \]

- Can answer the question:
  - “Are psychological intervention containing specific pairs of components effective (all other things being equal)?”
Model M4: Full Interaction Model

• Each possible combination of components has a distinct effect

\[
d_{\text{Int}} = \beta_{\text{Int}}
\]

• Same as standard network meta-analysis where each combination of components is a separate “treatment”

• Can answer the question:
  • “Are psychological intervention with a particular combination of components effective compared with usual care?”
  • … but only for the combinations that are included in the RCTs
Network plot: full interaction model
### Model Selection

- **Model M1**: Single effect
- **Model M2**: Additive main effects
- **Model M3**: Two way interactions
- **Model M4**: Full interaction

<table>
<thead>
<tr>
<th>Increased complexity</th>
<th>Reduced Assumptions</th>
<th>Less Generalisable</th>
<th>Less Precise Estimates</th>
</tr>
</thead>
</table>

- We prefer simpler models
- Compare measures of model fit (deviance, DIC)
- Compare heterogeneity estimates
- Inspect the credible intervals around the regression parameters, $\beta$
Results: Depression

M1: Single Effect  
(DIC=121.9, $\sigma=0.19$)

Any Psychological Intervention vs Usual Care

Standardised Mean Diff:

-0.23 (-0.36, -0.11)

M3: 2-way Interaction  
(DIC=121.6, $\sigma=0.11$)

M4: Full Interaction  
(DIC=123.2, $\sigma=0.11$)

M2: Main Effects  
(DIC=123.5, $\sigma=0.19$)

Caterpillar plot: $d$
Electronic Aids for Smoking Cessation
Chen et al HTA 2012 16:38, Madan (2014)

• What is the effectiveness of internet, PC and other electronic aids to help people stop smoking?
• Interventions defined as a combination of an electronic component and a non-electronic (control) component
<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
<th>Code</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>e0</td>
<td>Nothing (no electronic component)</td>
<td>c0</td>
<td>Nothing (no non-electronic component)</td>
</tr>
<tr>
<td>e1</td>
<td>Single generic component</td>
<td>c1</td>
<td>Generic self-help material</td>
</tr>
<tr>
<td>e2</td>
<td>Multiple generic components</td>
<td>c2</td>
<td>Brief advice</td>
</tr>
<tr>
<td>e3</td>
<td>Single tailored component</td>
<td>c3</td>
<td>Telephone or face to face counselling</td>
</tr>
<tr>
<td>e4</td>
<td>Single tailored component (+ generic component(s))</td>
<td>c4</td>
<td>Pharmacotherapy</td>
</tr>
<tr>
<td>e5</td>
<td>Multiple tailored components (± generic component(s))</td>
<td>c5</td>
<td>Counselling + pharmacotherapy</td>
</tr>
</tbody>
</table>
• 19 of the 35 possible combinations are included in the network
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Additive Model (M2)</th>
<th>Single Effect (M1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Electronic interventions:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c1 (self-help)</td>
<td>1.04 (0.94-1.14)</td>
<td></td>
</tr>
<tr>
<td>c2 (brief advice)</td>
<td>0.99 (0.84-1.17)</td>
<td></td>
</tr>
<tr>
<td>c3 (counselling)</td>
<td>0.95 (0.79-1.12)</td>
<td></td>
</tr>
<tr>
<td>c4 (pharmacotherapy)</td>
<td>1.00 (0.75-1.30)</td>
<td></td>
</tr>
<tr>
<td>c5 (counselling+pharmacotherapy)</td>
<td>0.85 (0.59-1.17)</td>
<td></td>
</tr>
<tr>
<td><strong>Electronic interventions:</strong></td>
<td></td>
<td>0.87 (0.83-0.92)</td>
</tr>
<tr>
<td>e1 (single generic)</td>
<td>0.89 (0.66-1.16)</td>
<td></td>
</tr>
<tr>
<td>e2 (multiple generic)</td>
<td>0.98 (0.78-1.21)</td>
<td></td>
</tr>
<tr>
<td>e3 (single tailored)</td>
<td>0.88 (0.83-0.93)</td>
<td></td>
</tr>
<tr>
<td>e4 (single tailored+generic)</td>
<td>1.02 (0.78-1.32)</td>
<td></td>
</tr>
<tr>
<td>e5 (multiple tailored)</td>
<td>0.85 (0.75-0.96)</td>
<td></td>
</tr>
</tbody>
</table>
Results Summary

- Overall there is evidence that electronic interventions are effective
- Single tailored and multiple tailored electronic interventions were effective
  - Majority of evidence was on these formats
CBT Interventions for Depression in Adults (INTERACT) Lopez-Lopez (2019)

- 76 studies, 6973 patients
## Results: Change in depression scores

<table>
<thead>
<tr>
<th>Intervention</th>
<th>sDiMC [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>0.20 [-0.91, 1.31]</td>
</tr>
<tr>
<td>Wait list</td>
<td>0.72 [0.09, 1.35]</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.34 [-1.21, 0.52]</td>
</tr>
<tr>
<td>F2F CBT</td>
<td>-1.11 [-1.62, -0.60]</td>
</tr>
<tr>
<td>Hybrid CBT</td>
<td>-1.06 [-2.05, -0.08]</td>
</tr>
<tr>
<td>Multimedia CBT</td>
<td>-0.59 [-1.20, 0.02]</td>
</tr>
</tbody>
</table>
Main Effects + Additive Components

**MAIN EFFECTS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>sDiMC [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>0.08 [-1.04, 1.23]</td>
</tr>
<tr>
<td>Wait list</td>
<td>0.75 [0.09, 1.41]</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.53 [-1.41, 0.35]</td>
</tr>
<tr>
<td>CBT</td>
<td>-1.77 [-2.57, -1.01]</td>
</tr>
</tbody>
</table>

**EFFECT MODIFIERS**

<table>
<thead>
<tr>
<th>Modification</th>
<th>sDiMC [95% CrI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimedia</td>
<td>0.36 [-0.24, 0.96]</td>
</tr>
<tr>
<td>Cognitive Techniques</td>
<td>0.38 [-0.21, 0.97]</td>
</tr>
<tr>
<td>Behavioural Activation</td>
<td>0.54 [-0.09, 1.16]</td>
</tr>
<tr>
<td>Psychoeducation</td>
<td>0.04 [-0.66, 0.75]</td>
</tr>
<tr>
<td>Homework</td>
<td>-0.21 [-0.90, 0.49]</td>
</tr>
<tr>
<td>Problem Solving</td>
<td>-0.04 [-0.67, 0.59]</td>
</tr>
<tr>
<td>Social Skills Training</td>
<td>0.55 [-0.37, 1.45]</td>
</tr>
<tr>
<td>Relaxation</td>
<td>0.03 [-0.81, 0.88]</td>
</tr>
<tr>
<td>Goal Setting</td>
<td>0.61 [-0.40, 1.62]</td>
</tr>
<tr>
<td>Final Session</td>
<td>-0.55 [-1.66, 0.54]</td>
</tr>
</tbody>
</table>

*Standardised Difference in Mean Change (compared to TAU)*
Standardised Difference in Mean Change (compared to TAU)
Summary of findings

• CBT interventions are effective in the reduction of depressive symptoms
• Results do not suggest a substantial difference between multimedia, hybrid, and face-to-face CBT
• No evidence that any content component increases treatment effectiveness
Combination Therapies

• Additive effect models can also be used for combination therapies and add-on treatments
  • Assuming no interactions
• E.g. in COPD (Kew et al 2014)
  • Long-acting beta-agonists (LABA)
  • Long-acting muscarinic antagonists (LAMA)
  • Inhaled corticosteroids (ICS)
  • Combined LABA+ICS
COPD: SGRQ 6 months: Additive effects?

Additive effect
Seems reasonable…
Roflumilast: Treatment network

In TA244: Roflumilast for the management of severe chronic obstructive pulmonary disease
Summary

• Component NMA models have the potential to identify active ingredients of complex interventions

• Additive models
  • allow more precise estimates than standard NMA
  • estimates for combinations not included in RCTs can be obtained
  • … but assume no interactions, which is difficult to verify in practice due to insufficient evidence

• Limited power to estimate additive effects (let alone interaction effects)
  • Need very rich evidence sources e.g. dismantling studies
References


