Modelling the effects of drug dose in hierarchical network meta-analysis models to account for variability in treatment classifications

Areti Angeliki Veroniki, MSc, PhD
C. Del Giovane, D. Jackson, S. E. Straus, S. Thomas, E. Blondal, K. Thavorn, A. C. Tricco

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Knowledge Translation Program,
Li Ka Shing Knowledge Institute,
St. Michael's Hospital,
Toronto, Canada

E-mail: VeronikiA@smh.ca
I have no actual or potential conflict of interest in relation to this presentation
Aims of the presentation

• To present approaches to model the effects of drug dosages in hierarchical network meta-analysis (NMA)
  • How can we model dose-effects in NMA while accounting for the drug-dose relationship?
• To present hierarchical NMA models accounting for effects of: 1) treatment, 2) strength (e.g., low, medium, high) of dose, and 3) specific dose
  • How do initial decisions on the network structure impact heterogeneity and inconsistency?
• To illustrate examples of the available approaches
  • Does the effect size vary across different dose levels?
  • Is there a pattern in dose-effects?
Network Meta-analysis (NMA)

NMA has become increasingly popular over the last two decades with ~500 publications

- In many conditions there are multiple treatments that could be considered
- When policy makers are considering what interventions to cover through health plans or what safety labels to put on medications, they need evidence from an NMA because this method uses all available RCTs for a specific clinical topic
- Clinicians and patients need to know the safest and most effective treatment dose for a particular situation

<table>
<thead>
<tr>
<th>Year</th>
<th>Temporal Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015*</td>
<td>10.5%</td>
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<tr>
<td>2014</td>
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<td>2013</td>
<td>18.3%</td>
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<td>2011</td>
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<td>2010</td>
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<tr>
<td>2009</td>
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<tr>
<td>2003</td>
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</tr>
<tr>
<td>2002</td>
<td>0.2%</td>
</tr>
<tr>
<td>2000</td>
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</tr>
<tr>
<td>1999</td>
<td>0.2%</td>
</tr>
<tr>
<td>1997</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

*2015 sample is not complete
Combining placebo-controlled trials to learn about toothpaste vs. rinse may yield erroneous results! Salanti et al JCE 2009

Typical approach: Choice between ‘lumping’ and ‘splitting’ methods

Splitting:
✓ Allows comparison between different treatment doses
✗ Ignores the relationship between doses that belong to the same intervention
✗ May lead to a relatively small number of studies across comparisons resulting in considerable uncertainty around the overall treatment effects
Common Dilemma in NMA...

Lumping:
✓ Increases the amount of evidence across comparisons and hence precision in treatment effects
✗ Ignores the different doses included in each intervention
✗ Cannot model studies that compare the same treatment at different doses
  • Researchers have to select a specific dose for the underlying treatment
  • If no other treatment is compared in the particular study, the study has to be excluded.

How do NMA authors deal with treatment doses?

219 (44%) of 494 NMAs published up to April 14, 2015 included different treatment doses in the network

Guidelines on modeling different dose-effects in NMA are imperative
Variance components added to each new level

RCTs comparing 2 treatment dosages

within-study variance

Meta-analysis

between-study variance

Network Meta-analysis

Usually we assume common between-study variance across dose comparisons

Categorizing doses into groups (e.g., Low, Medium, and High doses)

between-dose-category variance within treatment*

Categorizing doses into groups of treatments

between-dose variance within treatment
within dose category if doses are categorized into groups

*here the between dose variance is within dose-category (and not treatment)
Modelling dose-effects in NMA

Decision-makers are often interested in a treatment’s effectiveness at lower and higher doses. The potential dependence of treatment-effects of drug dose is an important issue for effectiveness and safety and is challenging in NMA because comparisons between interventions may vary in doses.

Hierarchical models can be used to address dose-effects in NMA and to facilitate the identification of the most effective treatment and optimal dose.
Modelling dose-effects in NMA

**Independent dose-effects**

*All dose-effects are unrelated*

- a) within-study and b) between-study variance across doses

**Random dose-effects within treatments**

*All dose-effects are related and exchangeable*\(^*\)

- a) within-study, b) between-study within dose level, and c) between-dose variance within treatment level

**Fixed dose-effects**

*All dose-effects are assumed equal within the same treatment*

**Random dose-effects within different dose categories**

*All dose-effects are related and exchangeable accounting for the dose-category they belong to*

- a) within-study, b) between-study within dose level, c) between-dose within-dose-category level, and d) between-dose-category variance within treatment level

\(^*\) Within the treatment they belong to

Del Giovane et al Stat Med 2013
Illustrative Examples

1. Serotonin 5-hydroxytryptamine 3 (5HT3) receptor antagonists to treat patients undergoing surgery

2. Anti-vascular endothelial growth factor (anti-VEGF) drugs to treat patients with wet age-related macular degeneration (AMD)

* All analyses have been performed in a Bayesian framework using OpenBUGS
Illustrative Example 1

Serotonin 5-hydroxytryptamine 3 (5HT3) receptor antagonists to treat patients undergoing surgery

• 5-HT3 receptor antagonists are commonly used to decrease nausea and vomiting for surgery patients
• Evidence shows that these agents may be harmful, but it is unclear whether there are certain doses that increase the risk of arrhythmia
• Clinicians and patients are interested in the safest treatment dose
• We used data from a published systematic review and NMA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>1mg, 2mg, 3mg, 4mg, 8mg, 16mg, 24mg</td>
</tr>
<tr>
<td>Granisetron</td>
<td>0.1mg, 1mg, 3mg</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>12.5mg, 25mg, 50mg, 100mg, 200mg</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>0.5mg, 2mg, 5mg</td>
</tr>
<tr>
<td>Ramosetron</td>
<td>0.3mg, 0.9mg</td>
</tr>
</tbody>
</table>

Aim
To estimate the relative safety of 5HT3 receptor antagonists at different dosages

Tricco et al BMC Medicine 2015
**Illustrative Example 1**

*5HT3 receptor antagonists to treat patients undergoing surgery*

- Patients of any age undergoing any type of surgery who were given a 5-HT3 receptor antagonist for nausea and/or vomiting
- Databases searched: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials; protocol registries and conference proceedings – up to January 2013
- One dichotomous outcome was considered to assess safety: arrhythmia – We will also assess efficacy using the vomiting outcome
- 29 RCTs were eligible after the screening process
- Exclusion:
  - ✓ Compared a combination of treatments against a single treatment (1 study).
  - ✓ Did not report the treatment dosages used (1 study).
- In total, 27 studies were included in the analysis

*Tricco et al BMC Medicine 2015*
5-HT$_3$ receptor antagonists for surgery

Arrhythmia: 27 studies, 8871 patients, 6 treatments, 21 doses

Tricco et al BMC Medicine 2015

Circles from outside in refer to:
1: Fixed Effects model
2: Random Effects (with dose consistency)
3: Random Effects (no dose consistency)
4: Independent Effects

1: Placebo
2: Ondansetron-Fixed
3: Ondansetron-1mg
4: Ondansetron-2mg
5: Ondansetron-3mg
6: Ondansetron-4mg
7: Ondansetron-8mg
8: Ondansetron-16mg
9: Ondansetron-24mg
10: Ondansetron-Fixed
11: Ondansetron-0.1mg
12: Ondansetron-1mg
13: Ondansetron-3mg
14: Dolasetron-Fixed
15: Dolasetron-12.5mg
16: Dolasetron-25mg
17: Dolasetron-50mg
18: Dolasetron-100mg
19: Dolasetron-200mg
20: Tropisteron-Fixed
21: Tropisteron-0.5mg
22: Tropisteron-2mg
23: Tropisteron-5mg
24: Ramosetron-Fixed
25: Ramosetron-0.3mg
26: Ramosetron-0.9mg

Veroniki et al JCE 2016
5-HT\textsubscript{3} receptor antagonists for surgery

<table>
<thead>
<tr>
<th>Common comparator: Placebo</th>
<th>OR (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dolasetron</strong></td>
<td></td>
</tr>
<tr>
<td>Fixed</td>
<td>0.74 (0.54, 1.03)</td>
</tr>
<tr>
<td>12.5mg</td>
<td>0.76 (0.40, 1.44)</td>
</tr>
<tr>
<td>25mg</td>
<td>0.79 (0.46, 1.31)</td>
</tr>
<tr>
<td>50mg</td>
<td>0.76 (0.51, 1.11)</td>
</tr>
<tr>
<td>100mg</td>
<td>0.75 (0.51, 1.10)</td>
</tr>
<tr>
<td>200mg</td>
<td>0.73 (0.48, 1.05)</td>
</tr>
</tbody>
</table>

| **Granisetron**             |             |
| Fixed                       | 0.84 (0.35, 2.33) |
| 0.1mg                       | 0.62 (0.14, 2.48) |
| 1mg                         | 0.81 (0.33, 2.19) |
| 3mg                         | 0.88 (0.35, 2.23) |

| **Ondansetron**             |             |
| Fixed                       | 0.90 (0.69, 1.18) |
| 1mg                         | 1.11 (0.54, 2.30) |
| 2mg                         | 0.92 (0.66, 1.30) |
| 3mg                         | 1.37 (0.44, 4.51) |
| 4mg                         | 0.91 (0.65, 1.32) |
| 8mg                         | 0.72 (0.19, 2.72) |
| 16mg                        | 0.77 (0.42, 1.33) |
| 24mg                        | 0.89 (0.64, 1.20) |

| **Ramosetron**              |             |
| Fixed                       | 1.20 (0.70, 2.11) |
| 0.3mg                       | 1.27 (0.53, 2.95) |
| 0.9mg                       | 1.20 (0.67, 2.18) |
| 1mg                         | 1.24 (0.67, 2.38) |
| 2mg                         | 1.16 (0.48, 2.78) |
| 3mg                         | 1.19 (0.66, 2.16) |
| 4mg                         | 1.24 (0.66, 2.40) |

| **Tropisetron**             |             |
| Fixed                       | 0.86 (0.44, 1.67) |
| 0.5mg                       | 0.75 (0.02, 7.20) |
| 2mg                         | 0.86 (0.42, 1.73) |
| 5mg                         | 0.86 (0.25, 2.59) |
| 10mg                        | 0.86 (0.43, 1.67) |
| 20mg                        | 0.85 (0.43, 1.75) |
| 30mg                        | 0.83 (0.33, 2.06) |
| 50mg                        | 0.85 (0.43, 1.63) |

Fixed Effects
Independent Effects
Random Effects (with dose consistency)
Random Effects (no dose consistency)
The design by treatment interaction model suggested consistency on both treatment ($\chi^2=2.46$, $P$-value=0.7829, $\tau^2=0.00$) and dose ($\chi^2=14.35$, $P$-value=0.6423, $\tau^2=0.00$) levels.
Illustrative Example 2

Anti-vascular endothelial growth factor (anti-VEGF) drugs to treat patients with wet age-related macular degeneration (AMD)

- Anti-VEGF drugs are injected into the eye where they inhibit the abnormal angiogenesis that underlies many retinal conditions associated with vision loss.
- It is unclear whether these agents have equivalent efficacy, and specifically whether there are certain doses that patients would benefit from when comparing these different drugs.

**Aim**
To estimate the relative efficacy of anti-VEGF agents at different dosages.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Abbreviation</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>PLAC</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>RANI</td>
<td>0.3mg, 0.5mg, 2mg,</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>BEVA</td>
<td>1.25mg, 2.5mg</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>AFLI</td>
<td>0.5mg, 2mg, 4mg</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>TRIAM</td>
<td>4mg</td>
</tr>
<tr>
<td>Photodynamic therapy with verteporfin</td>
<td>PDT</td>
<td>Standard fluence, reduced fluence</td>
</tr>
</tbody>
</table>
Illustrative Example 2

**Anti-VEGF drugs to treat patients with wet AMD**

- Adults (≥ 18 years) with wet AMD
- Databases searched: MEDLINE, Embase, Cochrane Central Register of Controlled Trials; Grey literature (trial protocols) – up to October 2015
- Two dichotomous outcomes were considered: vision gain & vision loss
- 35 RCTs were eligible after the screening process
- Exclusion:
  - compared the same treatment at the same dose (8 studies).
  - did not report vision gain outcome (3 studies) or vision loss outcome (3 studies).
- In total, 24 studies were included in the analysis for both outcomes
**Anti-vascular endothelial growth factor**

**Vision gain:** 24 studies, 9444 patients, 5 treatments, 11 doses

- BEVA
- RANI
- AFLI
- PLAC
- PDT

**Vision loss:** 24 studies, 8311 patients, 6 treatments, 12 doses

- BEVA
- RANI
- AFLI
- PLAC
- PDT

**Treatment Level**

- BEVA – 1.25 mg
- BEVA – 2.5 mg
- RANI – 2 mg
- RANI – 0.5 mg
- RANI – 0.3 mg
- PDT - reduced
- PDT - standard

**Dose Level**

- BEVA – 1.25 mg
- BEVA – 2.5 mg
- AFLI – 0.5 mg
- AFLI – 2 mg
- AFLI – 4 mg
- PLAC
- PDT - standard
Anti-vascular endothelial growth factor

Vision gain: 24 studies, 9444 patients, 5 treatments, 11 doses

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>OR (95%CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANI 0.3mg vs PLAC</td>
<td>8.46 (5.04,14.09)</td>
</tr>
<tr>
<td>RANI 0.5mg vs PLAC</td>
<td>8.45 (4.93,14.13)</td>
</tr>
<tr>
<td>RANI 2mg vs PLAC</td>
<td>7.93 (4.57,13.47)</td>
</tr>
<tr>
<td>RANI 2mg vs PLAC</td>
<td>7.72 (4.54,12.76)</td>
</tr>
<tr>
<td>BEVA 1.25mg vs PLAC</td>
<td>6.80 (3.63,12.26)</td>
</tr>
<tr>
<td>BEVA 2.5mg vs PLAC</td>
<td>6.70 (3.48,12.31)</td>
</tr>
<tr>
<td>BEVA 5mg vs PLAC</td>
<td>6.66 (3.24,13.08)</td>
</tr>
<tr>
<td>BEVA 10mg vs PLAC</td>
<td>6.33 (2.88,13.03)</td>
</tr>
<tr>
<td>AFLI 0.5mg vs PLAC</td>
<td>7.74 (3.65,15.58)</td>
</tr>
<tr>
<td>AFLI 2mg vs PLAC</td>
<td>7.65 (3.43,15.87)</td>
</tr>
<tr>
<td>AFLI 4mg vs PLAC</td>
<td>7.87 (3.74,15.25)</td>
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<tr>
<td>PDT vs PLAC</td>
<td>3.09 (1.42,7.59)</td>
</tr>
<tr>
<td>PDT-reduced vs PLAC</td>
<td>3.15 (1.35,8.05)</td>
</tr>
<tr>
<td>PDT-standard vs PLAC</td>
<td>3.13 (1.32,8.19)</td>
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<tr>
<td>PDT-standard vs PLAC</td>
<td>3.54 (1.23,11.00)</td>
</tr>
</tbody>
</table>
Anti-vascular endothelial growth factor - SUCRA

Vision gain: 24 studies, 9444 patients, 5 treatments, 11 doses

Treatment hierarchy according to the SUrface under the Cumulative RAiKing curve

Salanti JCE 2009; Veroniki et al JCE 2016

Circles from outside in refer to:
1st: Fixed Effects model
2nd: Random Effects (no dose consistency)
3rd: Random Effects (with dose consistency)
4th: Independent Effects
## Anti-VEGF - Vision Gain

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th>RE model with no dose consistency</th>
<th>RE model with dose consistency</th>
<th>Independent dose-effects with no dose consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau^2$</td>
<td>0.09</td>
<td>0.04</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>(95% CrI)</td>
<td>(0.02, 0.29)</td>
<td>(0.00, 0.23)</td>
<td>(0.00, 0.24)</td>
<td>(0.00, 0.29)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td></td>
<td>0.05</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>(95% CrI)</td>
<td></td>
<td>(0.00, 0.23)</td>
<td>(0.00, 0.33)</td>
<td></td>
</tr>
<tr>
<td>DIC</td>
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<td><strong>99.03</strong></td>
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<tr>
<td>$\bar{D}$</td>
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<td>57.58</td>
<td>58.86</td>
<td>59.06</td>
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<td>pD</td>
<td>40.54</td>
<td>41.45</td>
<td>40.32</td>
<td>43.37</td>
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<tr>
<td>Data points</td>
<td>55</td>
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</tr>
</tbody>
</table>

The design by treatment interaction model suggested consistency on the dose level: $(\chi^2=1.94, P\text{-value}=0.585, \tau^2=0.08)$ – Consistency cannot be assessed on the treatment level.

**Anti-vascular endothelial growth factor**

**Vision loss:** 24 studies, 8311 patients, 6 treatments, 12 doses

--

**Treatment Level**

**Treatment Comparison**
- RANI vs PLAC
- BEVA vs PLAC
- AFLI vs PLAC
- PDT vs PLAC
- TRIAM vs PLAC

**OR (95%CrI)**
- RANI-0.3mg vs PLAC: 0.11 (0.07, 0.16)
- RANI-0.5mg vs PLAC: 0.11 (0.07, 0.16)
- RANI-2mg vs PLAC: 0.09 (0.05, 0.19)
- BEVA-1.25mg vs PLAC: 0.10 (0.06, 0.17)
- BEVA-2.5mg vs PLAC: 0.10 (0.06, 0.17)
- AFLI-0.5mg vs PLAC: 0.10 (0.05, 0.20)
- AFLI-2mg vs PLAC: 0.10 (0.05, 0.20)
- AFLI-4mg vs PLAC: 0.10 (0.05, 0.20)
- PDT-reduced vs PLAC: 0.10 (0.06, 0.18)
- PDT-standard vs PLAC: 0.10 (0.06, 0.17)
- TRIAM-4mg vs PLAC: 0.10 (0.05, 0.20)

--

**Dose Level**

**Treatment Comparison**
- Treated better
- Placebo better

**OR (95%CrI)**
- RANI-0.3mg vs PLAC: 0.11 (0.07, 0.16)
- RANI-0.5mg vs PLAC: 0.11 (0.07, 0.16)
- RANI-2mg vs PLAC: 0.10 (0.06, 0.17)
- BEVA-1.25mg vs PLAC: 0.10 (0.07, 0.20)
- BEVA-2.5mg vs PLAC: 0.10 (0.07, 0.17)
- AFLI-0.5mg vs PLAC: 0.09 (0.05, 0.18)
- AFLI-2mg vs PLAC: 0.09 (0.05, 0.18)
- AFLI-4mg vs PLAC: 0.10 (0.04, 0.22)
- PDT-reduced vs PLAC: 0.10 (0.04, 0.22)
- PDT-standard vs PLAC: 0.10 (0.04, 0.22)
- TRIAM-4mg vs PLAC: 0.10 (0.04, 0.22)
Anti-vascular endothelial growth factor - SUCRA

**Vision loss:** 24 studies, 8311 patients, 6 treatments, 12 doses

*Treatment hierarchy according to the SUface under the Cumulative RAnking curve*

---

**Treatment Level**

- **PDT**
- **PLAC**
- **TRIAM**
- **AFLI**
- **RANI**
- **BEVA**

---

**Dose Level**

- **1st:** Fixed Effects model
- **2nd:** Random Effects (no dose consistency)
- **3rd:** Random Effects (with dose consistency)
- **4th:** Independent Effects

*Salanti JCE 2009; Veroniki et al JCE 2016*
### Anti-VEGF - Vision loss

<table>
<thead>
<tr>
<th></th>
<th>FE model</th>
<th>RE model with no dose consistency</th>
<th>RE model with dose consistency</th>
<th>Independent dose-effects with no dose consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau^2$ (95% CrI)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(0.00, 0.16)</td>
<td>(0.00, 0.17)</td>
<td>(0.00, 0.16)</td>
<td>(0.00, 0.17)</td>
</tr>
<tr>
<td>$\sigma^2$ (95% CrI)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>(0.00, 0.17)</td>
<td>(0.00, 0.17)</td>
<td>(0.00, 0.93)</td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td>97.57</td>
<td>98.70</td>
<td>96.93</td>
<td>98.44</td>
</tr>
<tr>
<td>$\bar{D}$</td>
<td>61.32</td>
<td>60.13</td>
<td>58.04</td>
<td>56.85</td>
</tr>
<tr>
<td>pD</td>
<td>36.25</td>
<td>38.57</td>
<td>38.9</td>
<td>41.59</td>
</tr>
<tr>
<td>Data points</td>
<td>54</td>
<td>54</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

The design by treatment interaction model suggested consistency on the dose level: $(\chi^2=1.17, P\text{-value}=0.761, \tau^2=0.00)$ – Consistency cannot be assessed on the treatment level

Summary...

Why is it important to model dose-effects in NMA?

- Modelling dose-effects in NMA and accounting for the intervention-dose relationship:
  - Adds to borrow strength in estimating dose-effects within treatment classes
  - Overcomes problems with sparse data in the treatment networks
  - Can incorporate studies that compare the same treatment at different doses
  - Allows the identification of not only the best treatment in a network, but also the most effective dose
  - Increases power compared to carrying out several independent subgroup analyses, lumping or extreme splitting approaches
  - May provide additional insight on heterogeneity, inconsistency, intervention ranking, and hence decision-making

But....

- Different approaches used to classify treatments or model dose-effects in a network may result in important variations in interpretations drawn from NMA
Summary...

But....

- The available approaches cannot model studies that compare combinations of treatments in a single node (e.g., A+B vs. C+D)

- Dose-effect models do not always explain inconsistency. Inconsistency may still be evident due to an imbalance in the distribution of effect modifiers across comparisons
  - NMA models require consistency in at least one (e.g., treatment) level. Consistency should be evaluated at each level it is assumed

- An IPD-NMA is the optimal approach to explore these factors. Hence, it is imperative to advance NMA models addressing dose-effects using IPD, improving interpretability of NMA results

- Studies are needed to establish and advance IPD-NMA addressing dose-effects to make results more useful for decision-making
Future Work

- Develop dose-response NMA models allowing to impose structural relationships between the basic parameters
  - Use reduced forms of standard NMA models where all doses and treatments are conceptualized as separate treatments (accounting for between study within dose level variance)
  - Potentially introduce fractional polynomials in these models

- Develop hierarchical models that relax the consistency assumption in dose and treatment levels
  - Use higher dimension design specific inconsistency parameters than the standard NMA models, so that all studies receive appropriate inconsistency parameters related to their treatment-doses

- Extend all models including the between-dose-category level (e.g., low, recommended, high category of doses)
  - We are currently working on the statistical code for the random dose-effects within different dose categories model

- Extend dose-response NMA models including IPD.
References...

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E-mail: VeronikiA@smh.ca