Hierarchical network meta-analysis models accounting for variability in nodes by treatment, dosage-category and single dosage

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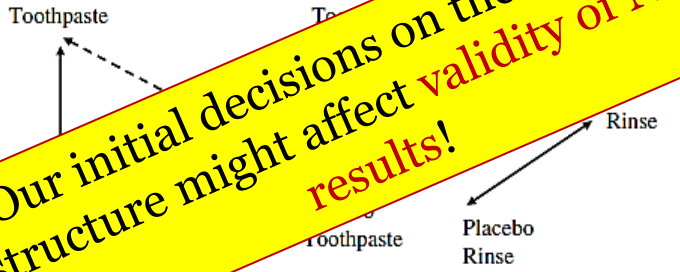
Common Dilemma in NMA…

Combining placebo-controlled trials to learn about toothpaste vs. ri… may yield erroneous resu…

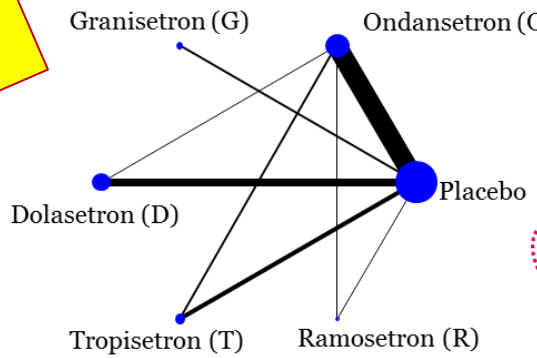


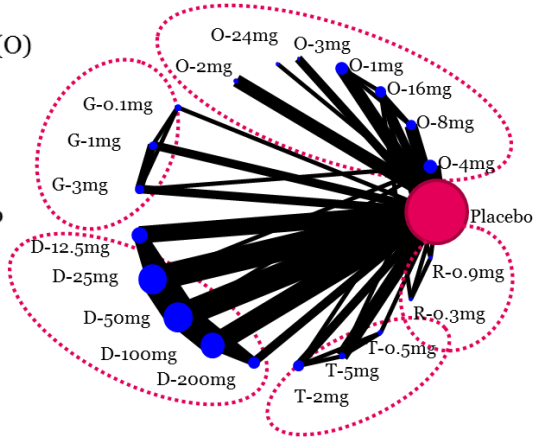
…ation of violation of a network assumption because of …lacebo treatments.

Salanti et al JCE 2009

Our initial decisions on the network structure might affect validity of NMA results!

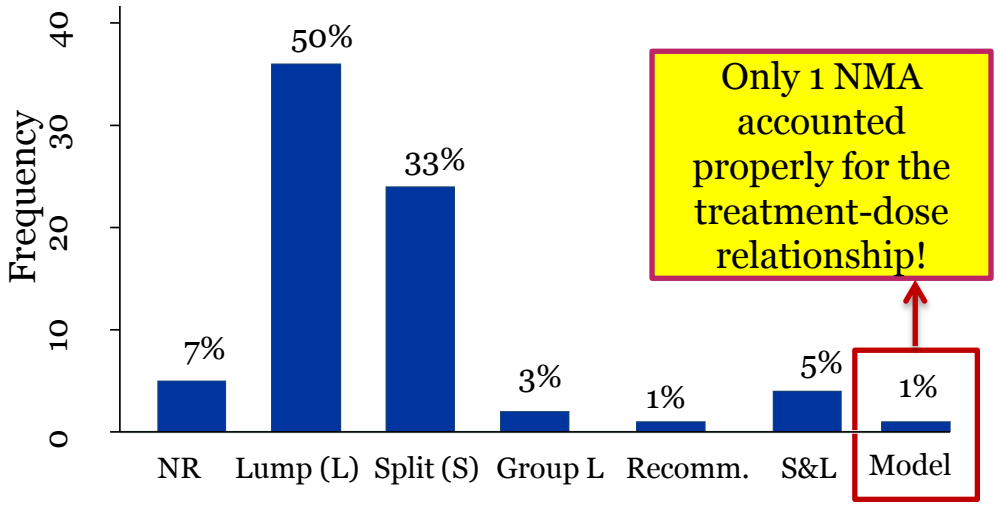
Lumping or splitting nodes?





How do NMA authors deal with treatment doses?

74 (40%) of 185 NMAs published until the end of 2012 included different treatment doses in the network.

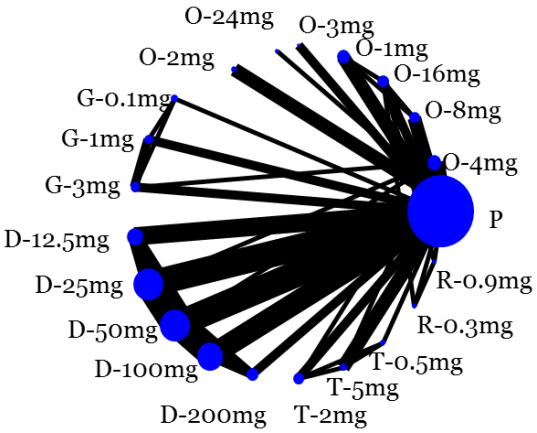


Modeling dose-effects in NMA

Independent dose-effects

All dose-effects are unrelated

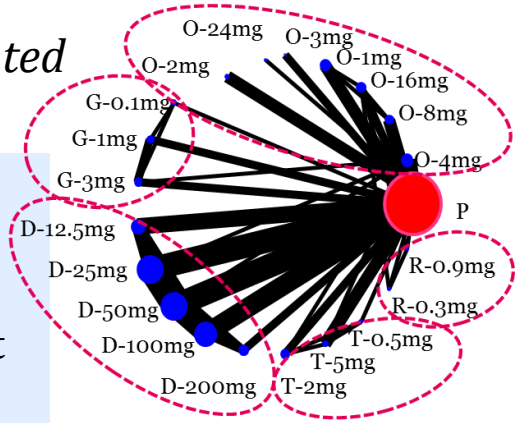
a) within-study and b) between-study variance between doses



Random dose-effects

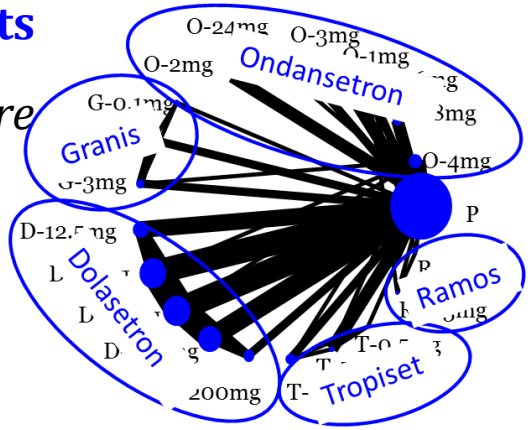
Dose-effects are related and exchangeable

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



Fixed dose-effects

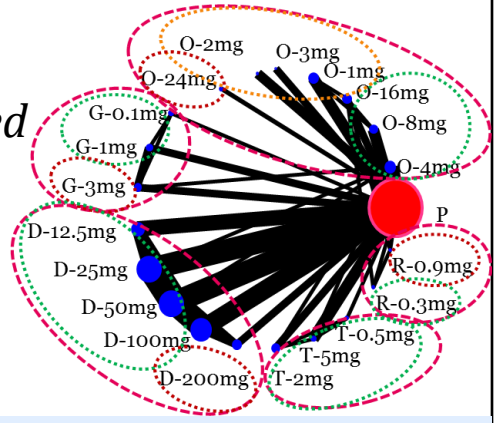
All dose-effects are assumed equal within the same treatment



a) within-study and b) between-study variance within dose

Random dose-effects within different dose categories

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



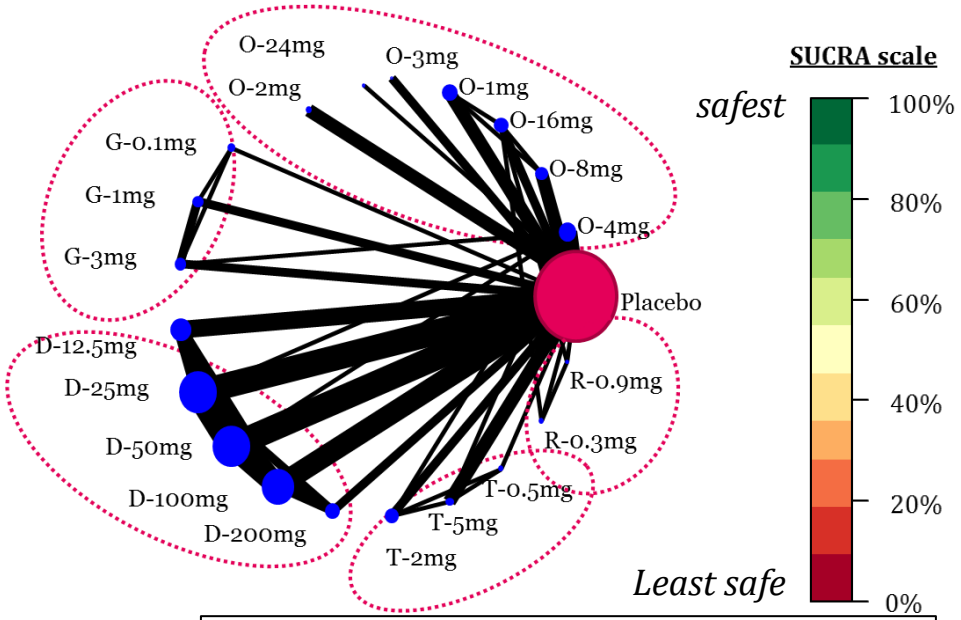
a) within-study, b) between-study within dose, c) between-dose within-dose-category, and d) between-dose-category within-treatment variance

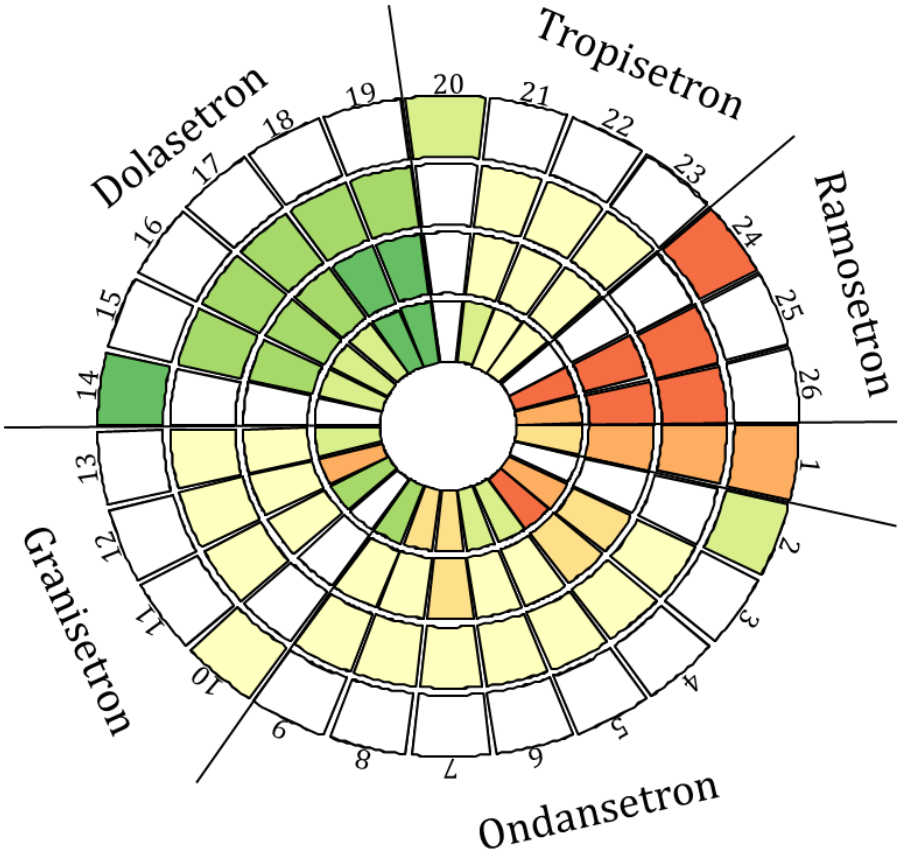
Del Giovane et al Stat Med 2013

Illustrative example - Dataset

Arrhythmia – 5HT3 surgery: 27 studies, 8871 patients, 6 treatments, 21 doses

Tricco et al BMC Medicine 2015





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

Circles from outside in refer to:

A: Fixed Effects model

B: Random Effects (with dose consistency)

C: Random Effects (no dose consistency)

D: Independent Effects

Summary

- Different approaches used to classify treatments in a network may result in important variations in interpretations drawn from 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
  - Provides additional insight on heterogeneity, inconsistency, intervention ranking, and hence decision-making