Limitations of Network Meta-Analyses

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Network Meta-Analysis of 15 Antipsychotic Drugs in Schizophrenia (212 studies, 43,049 participants)

Which drug is better?
Considerations

Is the question posed by the network meta-analysis clear?

- Whose perspective is being addressed?
  - Patient, clinician, payer, public health (which country?)
- Is the question pragmatic or explanatory?
- Is the question related to efficacy, safety, risk:benefit, economic value?
- What is the population of interest? (Was it comprehensively studied?)
- What is the outcome of interest?
- What is the setting of interest? (Developed or Developing World?)
- Who is to apply the treatment? (How much training is necessary?)
- To whom does the result generalize?
- **Is the question posed by the network meta-analysis completely prespecified?** (Are adjustments for multiplicity applied?)
Considerations

Are the individual study questions clear?

- Whose perspective is being addressed?
  - Patient, clinician, payer, public health (which country?)
- Is the question pragmatic or explanatory?
- Is the question related to efficacy, safety, risk:benefit, economic value?
- What is the population of interest?
- What is the outcome of interest?
- What is the setting of interest? (Developed or Developing World?)
- Who is to apply the treatment? (How much training is necessary?)
- Are the study questions the same across studies being evaluated?
  - (Clozaril Study 30 vs InterSePT vs more recent studies)
- Are definitions of key terms the same? (e.g. relapse, remission)
- How are the primary study questions related to the meta-analysis question?
Considerations

Was the **population studied** the same across studies included in the network meta-analysis?

– Similar inclusion/exclusion criteria?
– Was it same stage of illness?
– Drawn from the same population base? (Time and geography)
– Was it same subpopulation? (Substance abusing or not?)
– Was the baseline severity of illness similar?
Considerations

Was **methodology/design** adequate and similar across studies?

- Was the methodology appropriate for the study question?
  - Pragmatic analyses applied to an explanatory question
- What is duration of trial? (Days, Weeks, Months, Years)
- What were the study comparators? Did the comparators influence inclusion in the trial?
- Were the doses optimized for each drug equivalently? (CATIE study)
- What were prior treatments and how much and how recent was the switch to the novel treatment?
- Were the formulations the same?
- In what countries were the studies done?
- What was the treatment environment and was it equivalent across studies?
- Did the studies include similar treatment milieu? (cognitive therapy, family education)
- What co-morbidities were allowed?
- What concomitant medications were allowed?
Considerations

Was the conduct of the study adequate?
• Was the sample collected deviant from that allowed by the selection criteria? (PRIDE study)
• Was adherence the same across treatment arms?
• Did the subjects receive and take the medicine as prescribed in the protocol?
• Were there deviations from the protocol? (Do we know what they were?)
• Were dropouts equivalent across treatment arms?

KEY PRINCIPLE: There are a thousand reasons why a study might fail....far fewer reasons allow for a successful study
Considerations

**Was the quality of the analyses completed for the study adequate?**

- Was the analysis being considered for the meta-analysis consistent with the primary analysis of the original analysis?
- What were the biases of the studies included and how were they addressed?
  - Self selection bias for study inclusion
  - Rater bias
  - Bias related to treatment setting or time of study
  - Patient bias (fraud)
  - Biases related to the duration of the study?
- How well are biases addressed?
- What is level of data missingness? How was this addressed?
- Do outliers influence or drive the primary results?
- Were the results reviewed by regulatory authorities?

**KEY PRINCIPLE:** There are a thousand reasons why a study might fail....far fewer reasons allow for a successful study
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- At which doses?
- In which subpopulation?
- With which concomitant medications?
- In which country?
- Over what period of follow up?
- Which drug is better?
- For which outcomes?
- In which setting?
Network Meta-Analysis is Not.....
Network Meta-Analysis is more like.....

Does this animal have any abdominal deformities?
Network Meta-Analysis is more like.....

Does this animal have an injured limb?
Network Meta-Analysis is more like.....

Does this animal have an injury to the skull?
Network Meta-Analysis is more like…..

Does this animal have an injured limb?
Network Meta-Analysis is more like.....

Does this animal have any abdominal abnormalities?
Network Meta-Analysis is more like.....

Does this animal have a leg injury?
Network Meta-Analysis is more like.....

Does this animal have an injury to the skull?
Network Meta-Analysis is more like.....

META-ANALYTIC QUESTION: What animal was this?
Network Meta-Analysis is more like.....

What animal was this?
Network Meta-Analysis is more like.....

What animal was this?
Network Meta-Analysis is more like…..

What animals were these?
Conclusion

*Network meta-analyses and mixed treatment comparisons represent a valuable tool for aiding decision-making but...*
Conclusion

Network meta-analyses and mixed treatment comparisons represent a valuable tool for aiding decision-making but they must be reviewed and interpreted with caution.
Thanks for your attention!