NMA Learning Live Webinar series

Question formulation and protocol development for systematic reviews with network meta-analysis

Anna Chaimani

Research Center of Epidemiology and Statistics Sorbonne Paris Cité (CRESS-UMR1153), Université de Paris, Inserm, France

18 November 2019

Acknowledgements: Georgia Salanti, Julian Higgins, Deborah Caldwell, Tianjing Li

Meta-analysis in the literature

- Systematic reviews and meta-analyses of randomized controlled trials have "*transformed medicine*"
  - Establish evidence-based practice
  - Resolve contradictory research outcomes
  - Support research planning and prioritization

- Massive production of meta-analyses assessing healthcare interventions
  - More than 10,000 meta-analyses of RCTs per year

Donnelly et al., ***Nature*** *2018*
Sutherland et al. ***Nature*** *2018*

Limitation of pairwise meta-analysis

Example: Antidepressants for major depression

Paroxetine versus other anti-depressive agents for depression

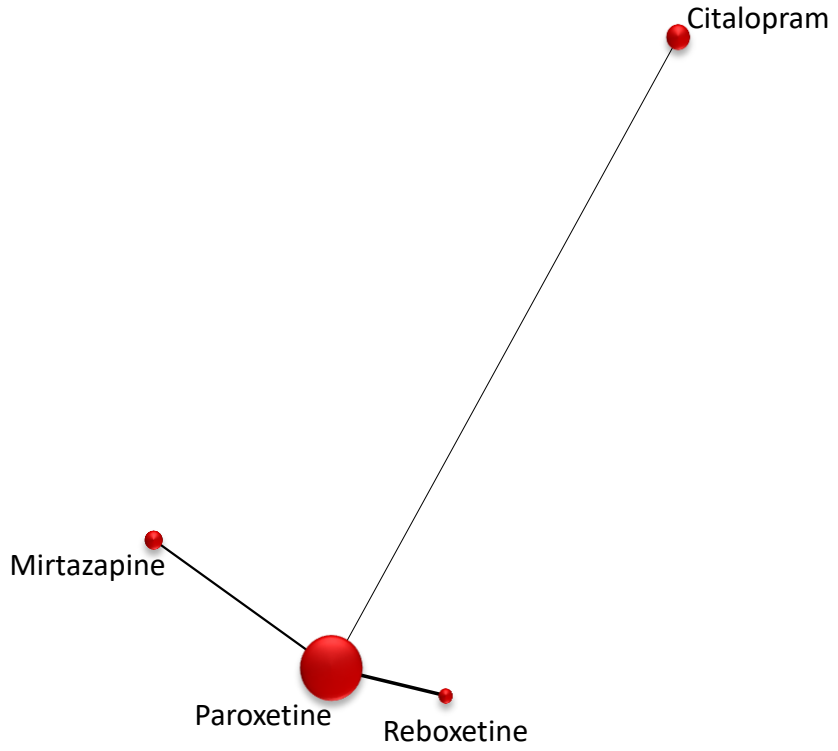
Marianna Purgato[1], Davide Papola[1], Chiara Gastaldon[1], Carlotta Trespidi[1], Laura R Magni[2], Carla Rizzo[3], Toshi A Furukawa[4], Norio Watanabe[5], Andrea Cipriani[6], Corrado Barbui[1]

"Paroxetine was more effective than reboxetine…"

"…less effective than mirtazapine"

"…less effective than citalopram"

Purgato et al. ***Cochrane Database Syst Rev*** *2014*



Limitation of pairwise meta-analysis

Example: Antidepressants for major depression

Paroxetine versus other anti-depressive agents for depression

Marianna Purgato[1], Davide Papola[1], Chiara Gastaldon[1], Carlotta Trespidi[1], Laura R Magni[2], Carla Rizzo[3], Toshi A Furukawa[4], Norio Watanabe[5], Andrea Cipriani[6], Corrado Barbui[1]

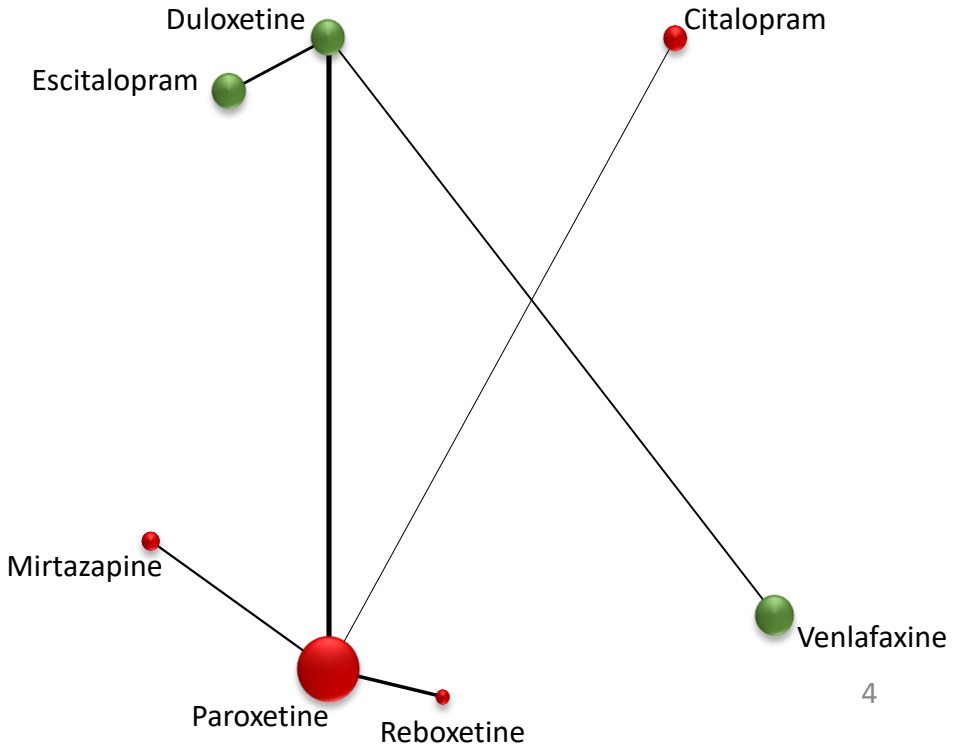
Duloxetine versus other anti-depressive agents for depression

Andrea Cipriani[1], Markus Koesters[2], Toshi A Furukawa[3], Michela Nosè[4], Marianna Purgato[1], Ichiro M Omori[5], Carlotta Trespidi[1], Corrado Barbui[1]

"…no statistically significant differences in efficacy when compared with other antidepressants…"

"…when compared with escitalopram or venlafaxine, there was a higher drop-out rate…"

"…more adverse events than paroxetine…"



Cipriani et al. ***Cochrane Database Syst Rev*** *2012*

From pairwise to network meta-analysis

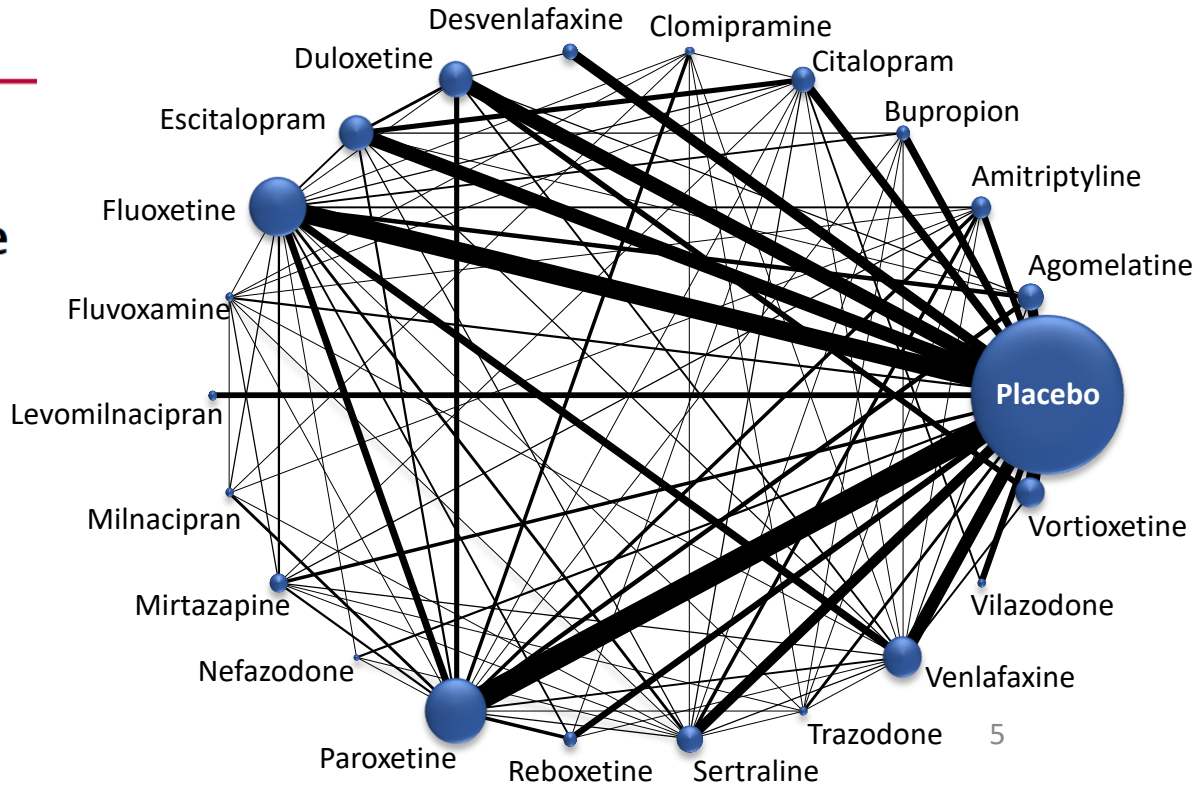
Example: Antidepressants for major depression

The most critical question raised by patients and clinicians at the point of care is

"what is the drug of choice for the given condition?"

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

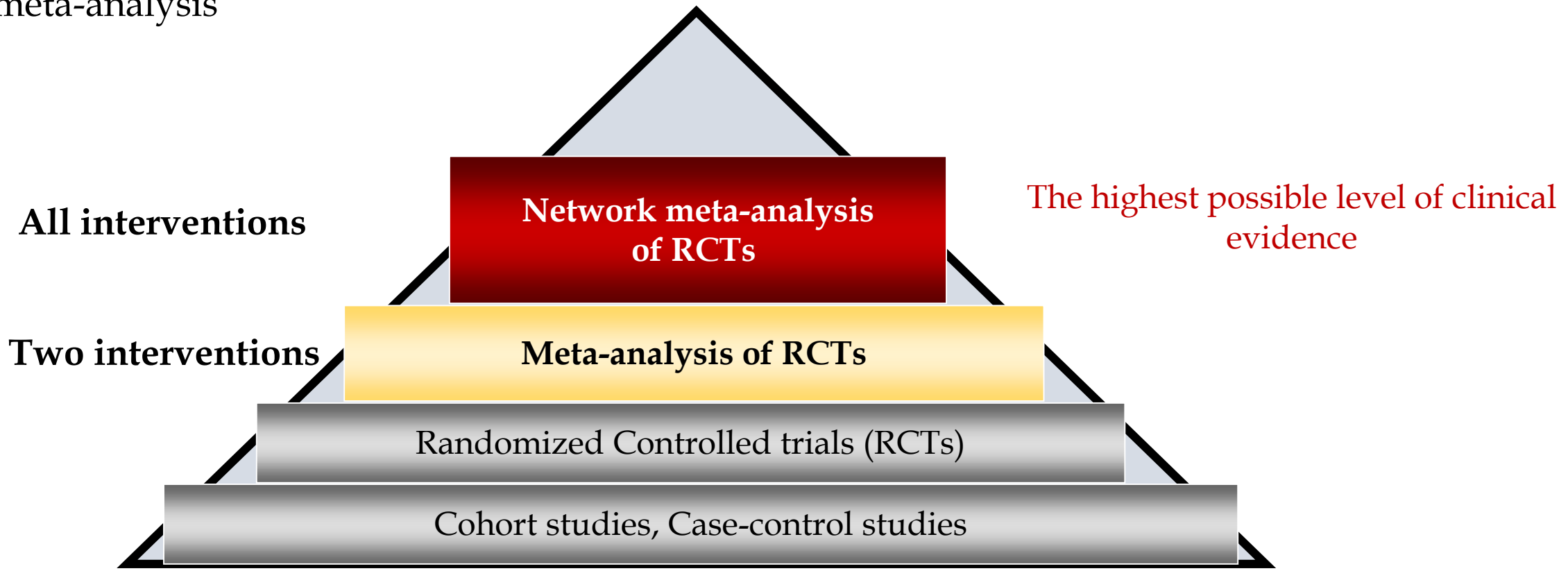
Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*



Cipriani et al. ***Lancet*** *2018*

Network meta-analysis in medical research

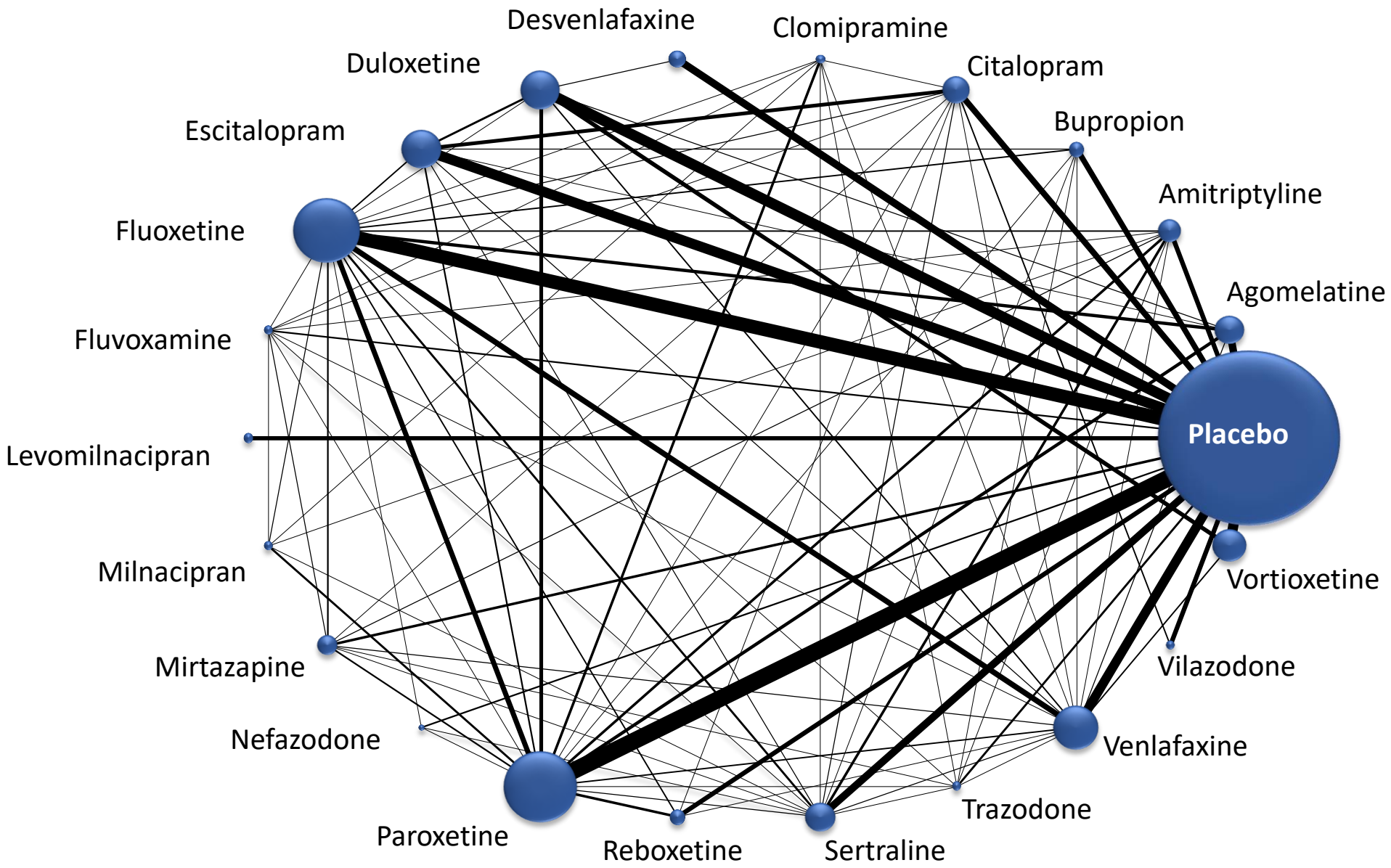
WHO (World Health Organization) guidelines now rely whenever possible on network meta-analysis



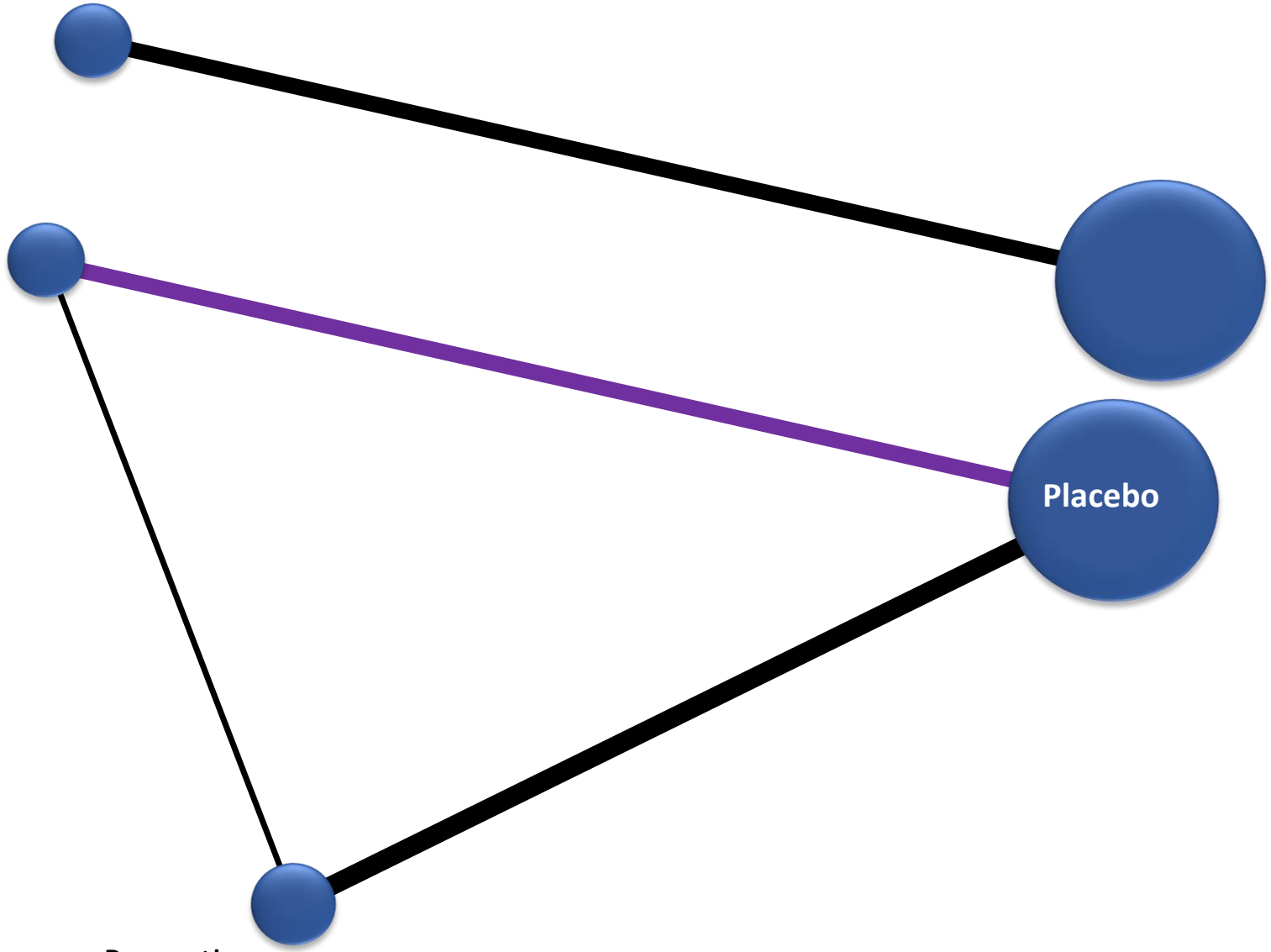
The highest possible level of clinical evidence

Faltinsen et al. ***BMJ Evid Based Med*** *2018*
Leucht et al. ***Eur Arch Psychiatry Clin Neurosci*** *2016*

Indirect and mixed effects



Indirect and mixed effects

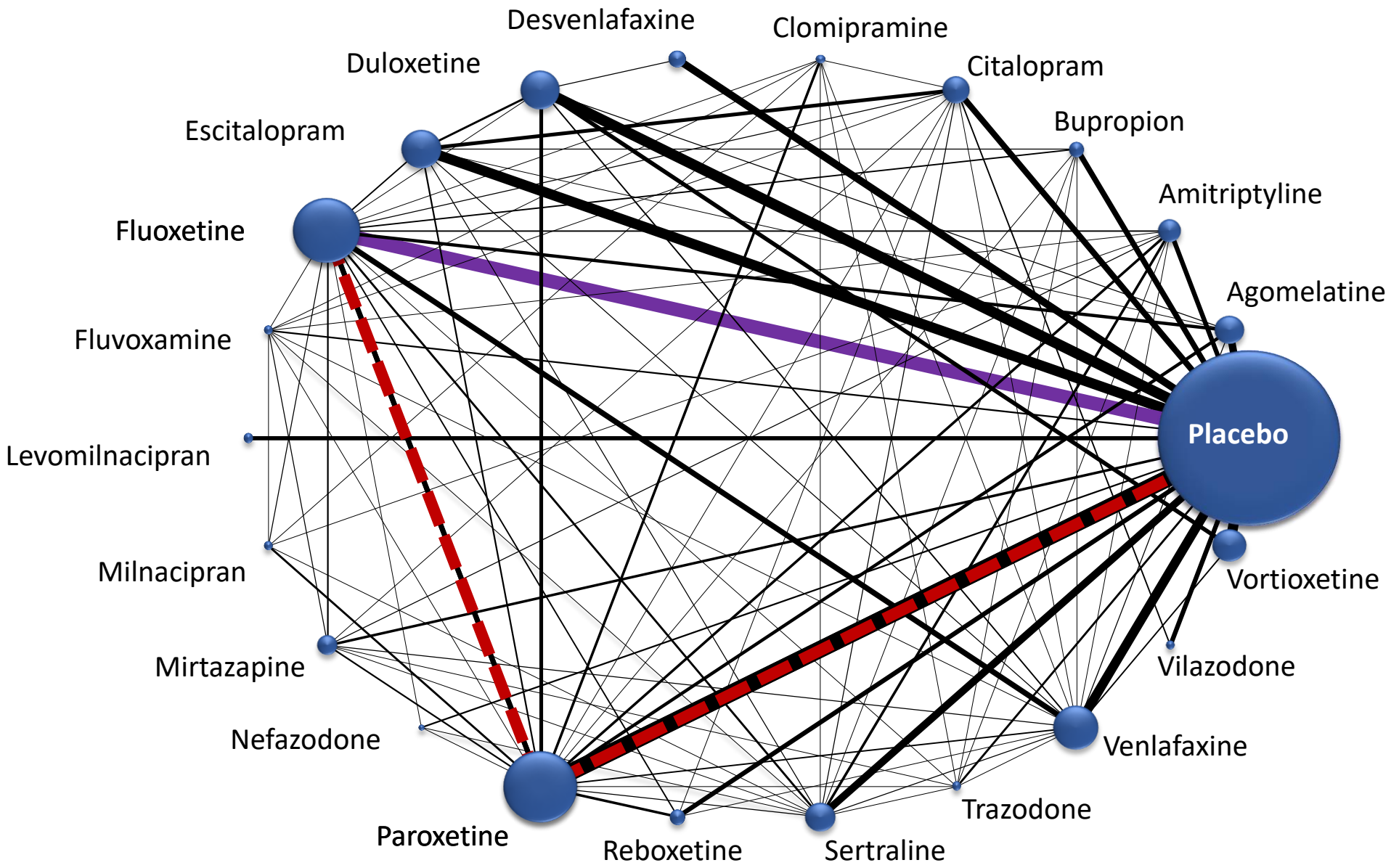


Indirect effect

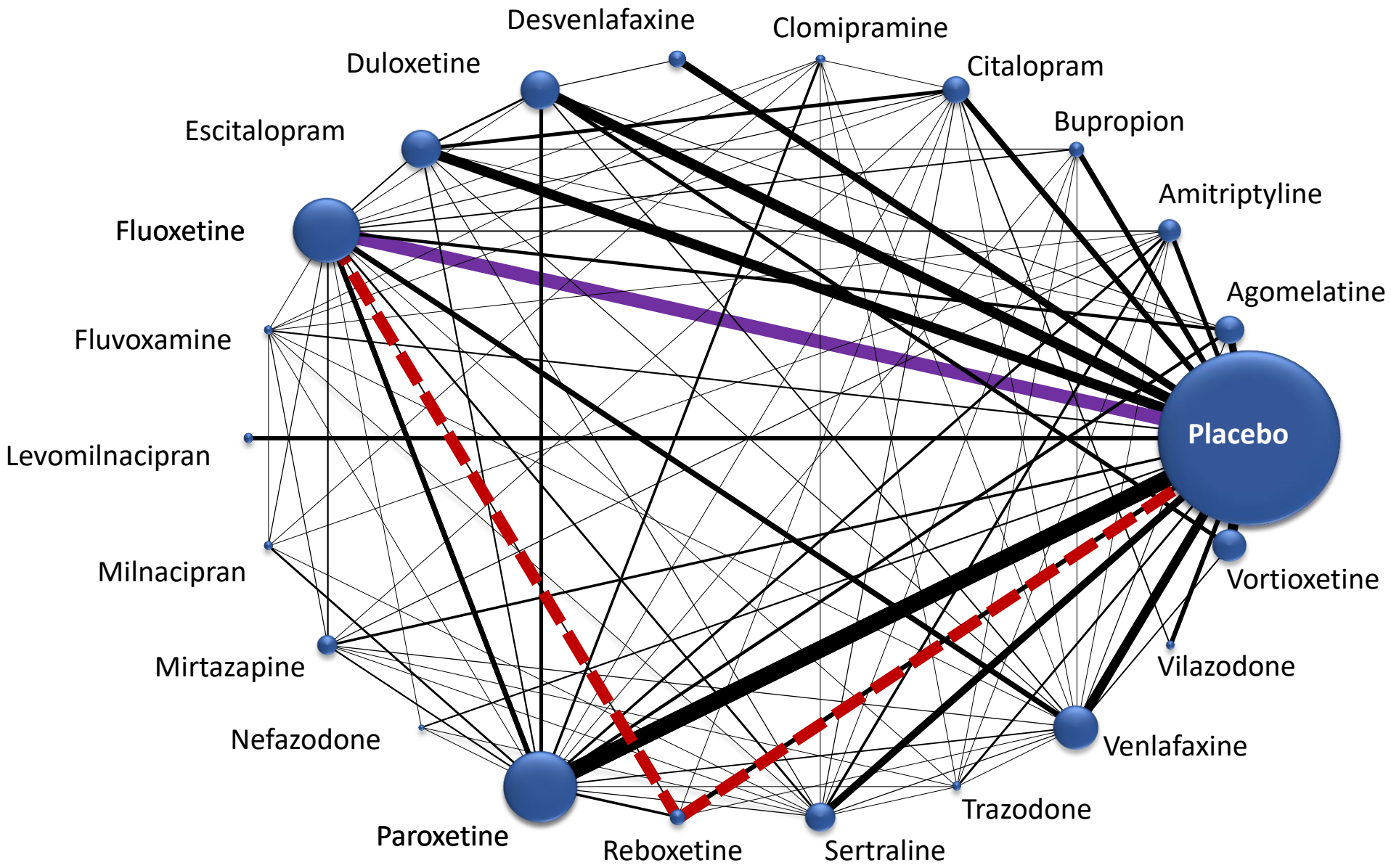
Direct effect

Mixed effect

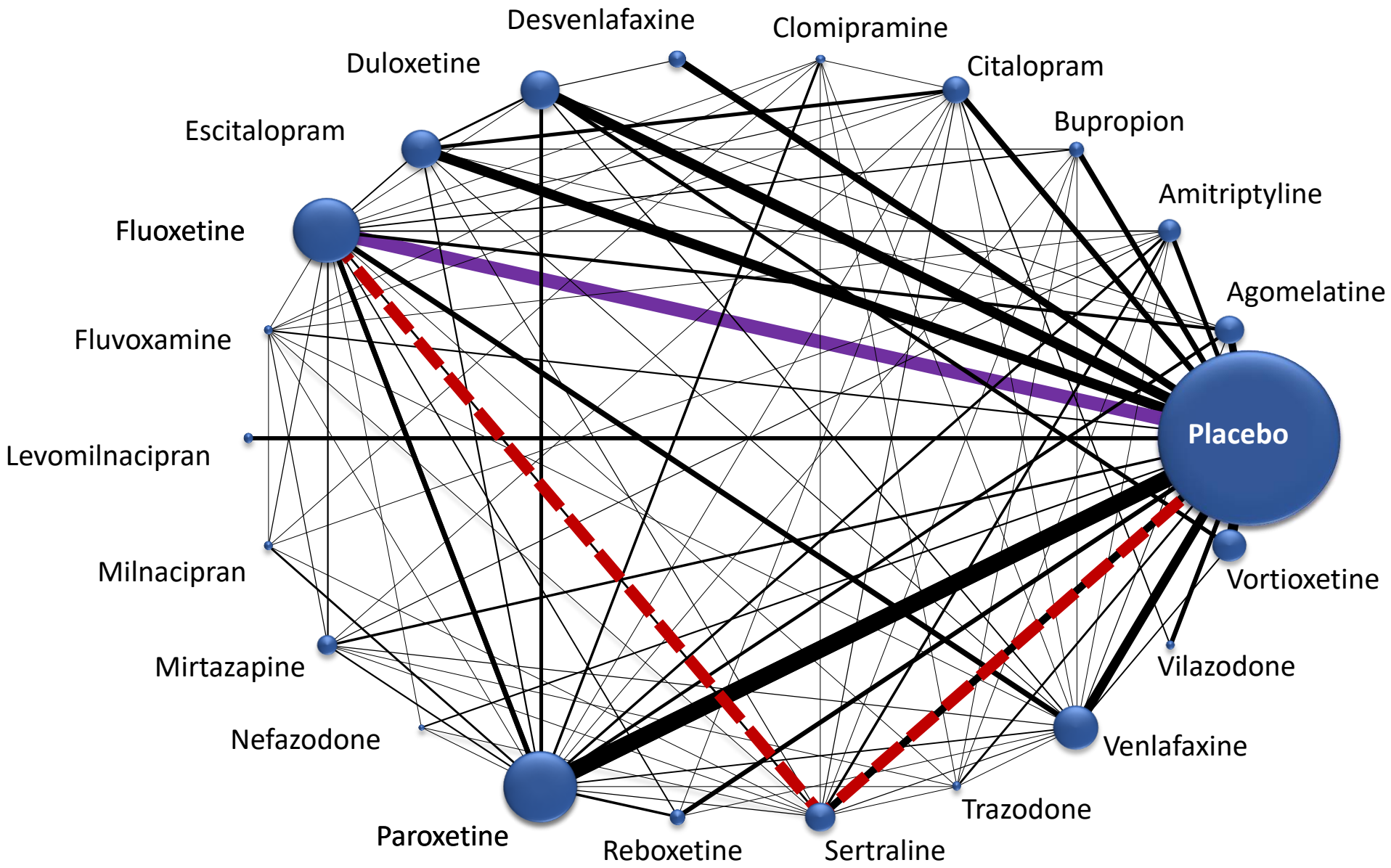
Indirect and mixed effects



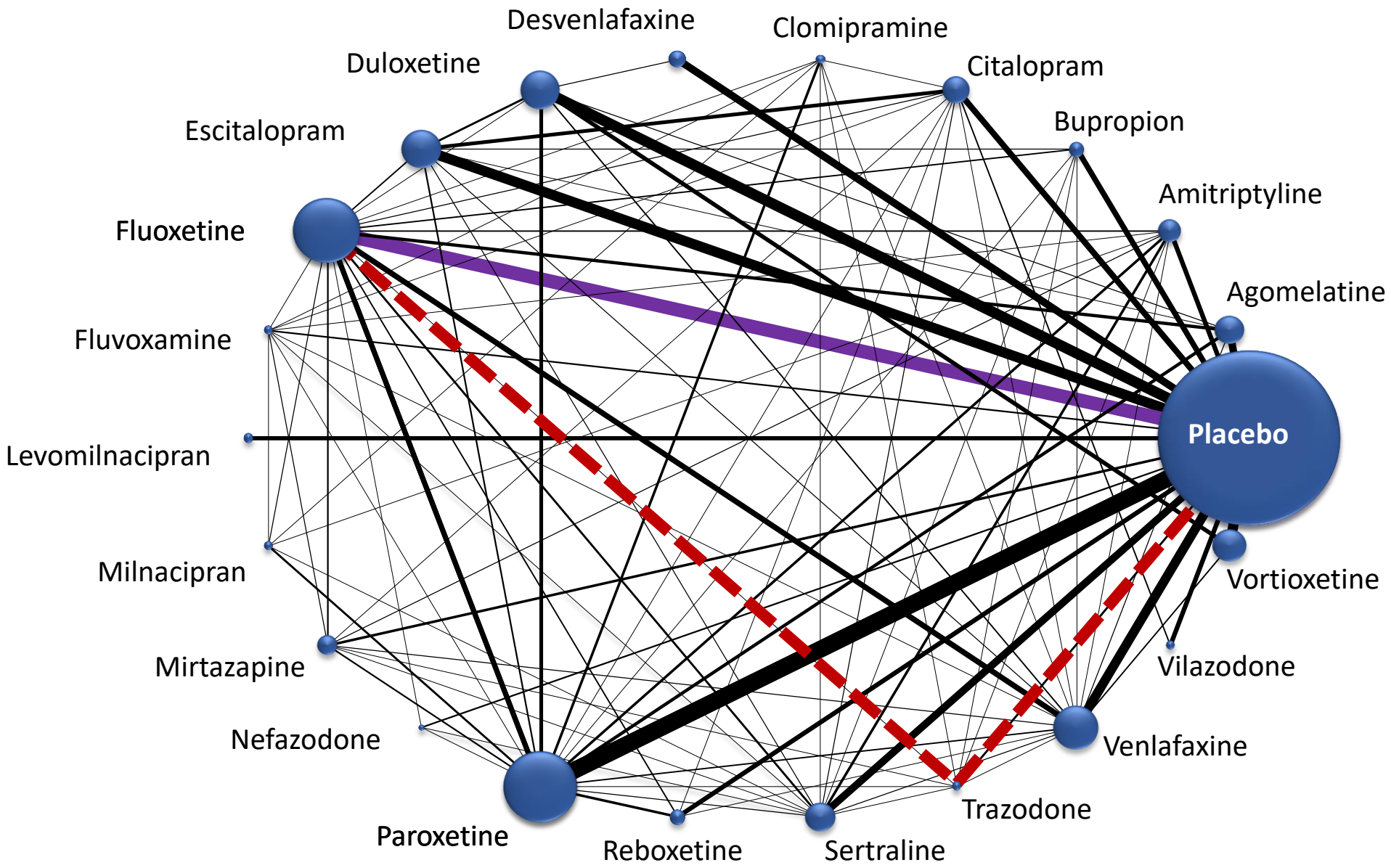
Indirect and mixed effects



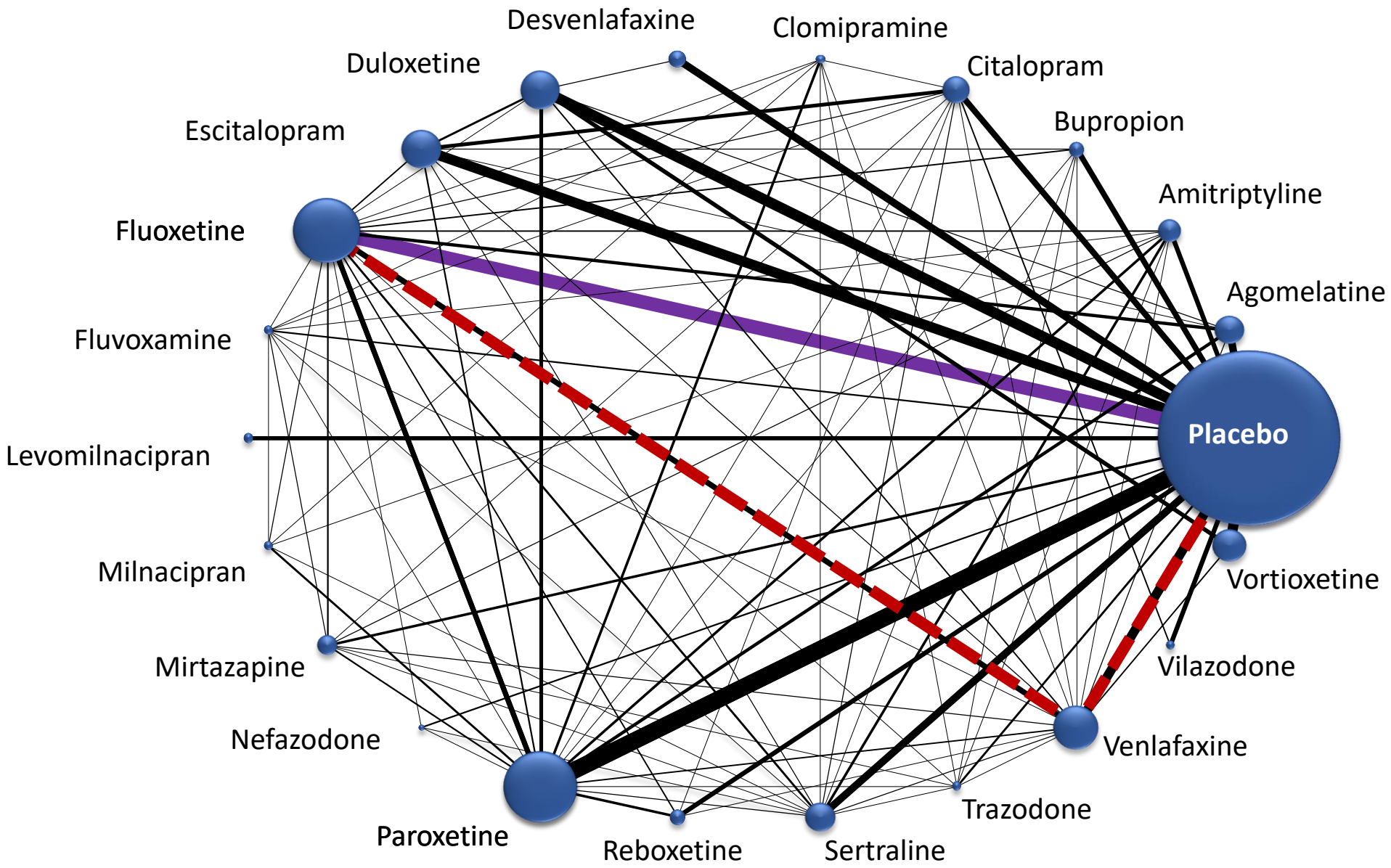
Indirect and mixed effects



Indirect and mixed effects



Indirect and mixed effects



Anecdotal evidence

- NMA projects are long, cumbersome and challenging
- Writing the protocol is a valuable opportunity to get things right from the start and get to know your collaborators

- **It involves**
  - long discussions (and disagreement!) between clinical experts
  - even longer discussions between statisticians and clinicians

- **It ensures that**
  - all needed data will be extracted and formatted in a convenient way
  - all team members learn to 'speak the same language'

- **Updating the evidence**
  - much much easier and quicker

Systematic review protocols with multiple interventions

A RevMan template for NMA protocols is under preparation

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 83 (2017) 65–74

Journal of Clinical Epidemiology

Additional considerations are required when preparing a protocol for a systematic review with multiple interventions

Anna Chaimani[a,*], Deborah M. Caldwell[b], Tianjing Li[c], Julian P.T. Higgins[b], Georgia Salanti[a,d,e]

[a]*Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, University Campus, Ioannina 45110, Greece*
[b]*School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK*
[c]*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E6011, Baltimore, MD 21205, USA*
[d]*Institute of Social and Preventive Medicine (ISPM), University of Bern, Finkenhubelweg 11, Bern 3012, Switzerland*
[e]*Institute of Primary Health Care (BIHAM), University of Bern, Gesellschaftsstrasse 49, Bern CH-3012, Switzerland*

Accepted 30 November 2016; Published online 11 January 2017

Abstract

Objectives: The number of systematic reviews that aim to compare multiple interventions using network meta-analysis is increasing. In this study, we highlight aspects of a standard systematic review protocol that may need modification when multiple interventions are to be compared.

Study Design and Setting: We take the protocol format suggested by Cochrane for a standard systematic review as our reference and compare the considerations for a pairwise review with those required for a valid comparison of multiple interventions. We suggest new sections for protocols of systematic reviews including network meta-analyses with a focus on how to evaluate their assumptions. We provide example text from published protocols to exemplify the considerations.

Conclusion: Standard systematic review protocols for pairwise meta-analyses need extensions to accommodate the increased complexity of network meta-analysis. Our suggested modifications are widely applicable to both Cochrane and non-Cochrane systematic reviews involving network meta-analyses.

Setting the rational for the review

- *Title: Identify the review as one that compares multiple interventions*

- **Clarify why a NMA is necessary**
  - lack of (many) direct comparisons between the treatments of interest
  - aim to comprehensively rank all treatments

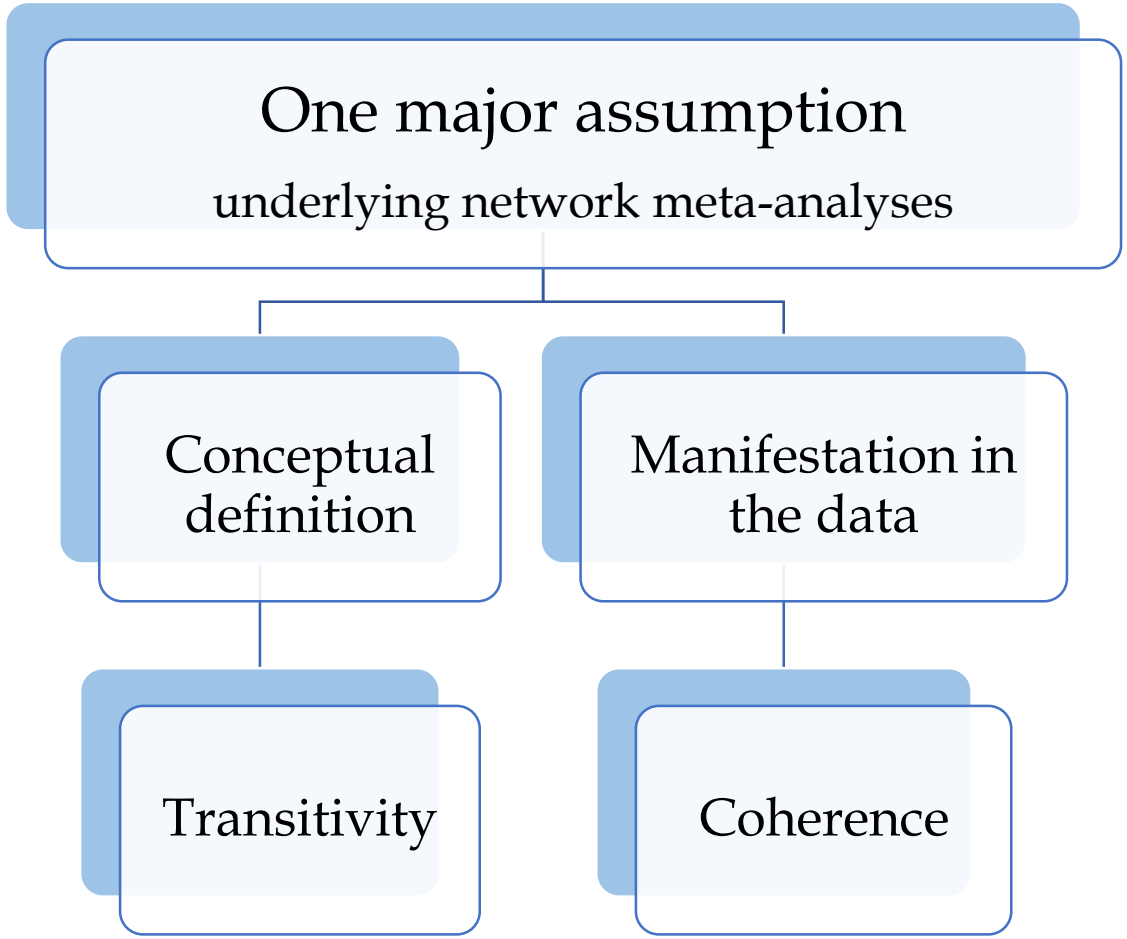
- *Example: Safety of antiepileptic drugs:*

"Some AEDs have been associated with increased risk of harm to the fetus and infants. […] many studies have produced inconsistent findings regarding harm to the fetus and infant with use of other agents. As such, our objective is to evaluate the comparative safety of AEDs for infants and children who were exposed in utero or during breastfeeding through a systematic review and network meta-analysis"

Tricco et al. ***Syst Rev*** *2014*

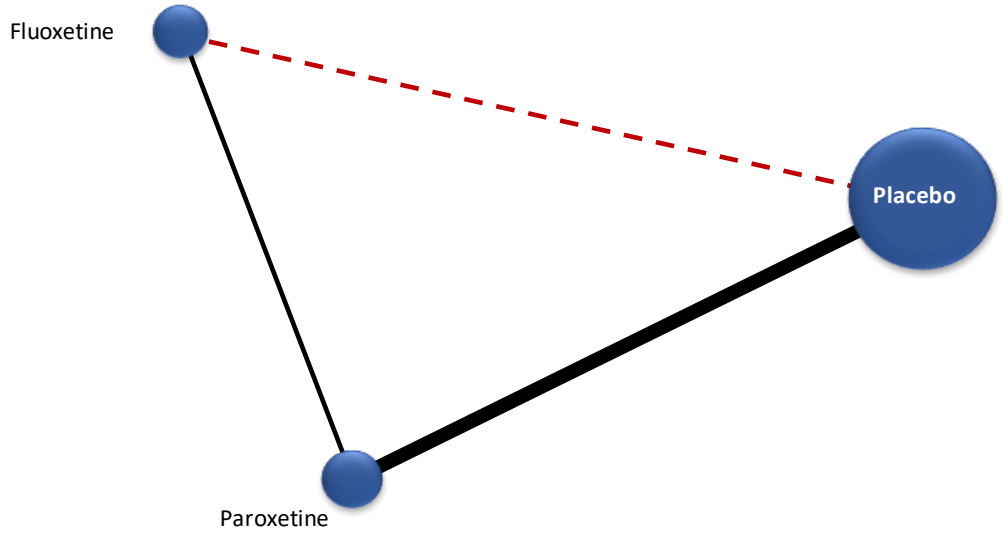
Frame the research question

- **Define the PICO**
  - Keep in mind the transitivity assumption!



Transitivity

The underlying assumption when B versus C is calculated *indirectly* is that we can learn about B versus C via A.

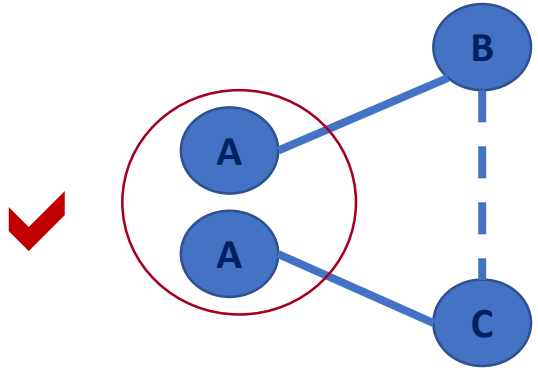


Validity depends on **transitivity** of treatment effects across trials making different treatment comparisons

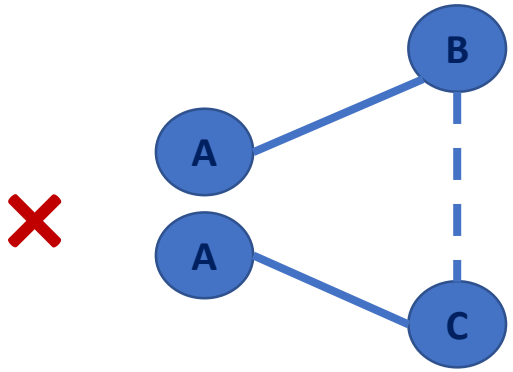
advantage of B over C =
advantage of B over A + advantage of A over C

Requires studies to be similar in ways other than the treatments being compared

Ways of thinking about transitivity…



Treatment A must be similar when it appears in AB and AC trials



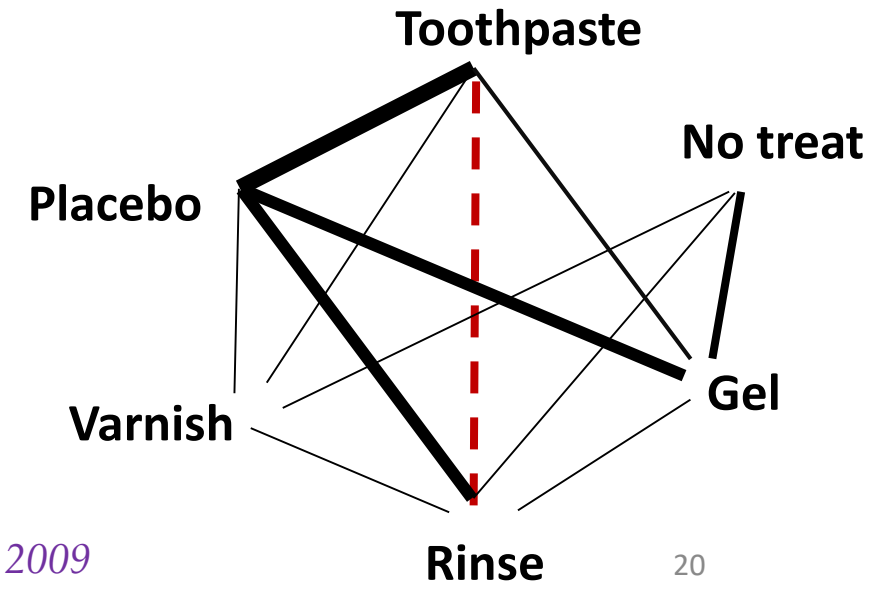
For example, is it plausible

- when A is placebo given in different forms (e.g. injection versus pill)?
- when A is a drug given in different doses?

Ways of thinking about transitivity…

- **Example:** When comparing different fluoride treatments, comparison between fluoride toothpaste and fluoride rinse can be made via placebo
  - However, placebo toothpaste and placebo rinse might not be comparable as the mechanical function of brushing might have a different effect on the prevention of caries
  - If this is the case, the transitivity assumption is doubtful

The definition of the nodes in the treatment network is a **challenging issue**



Salanti et al. JCE 2009

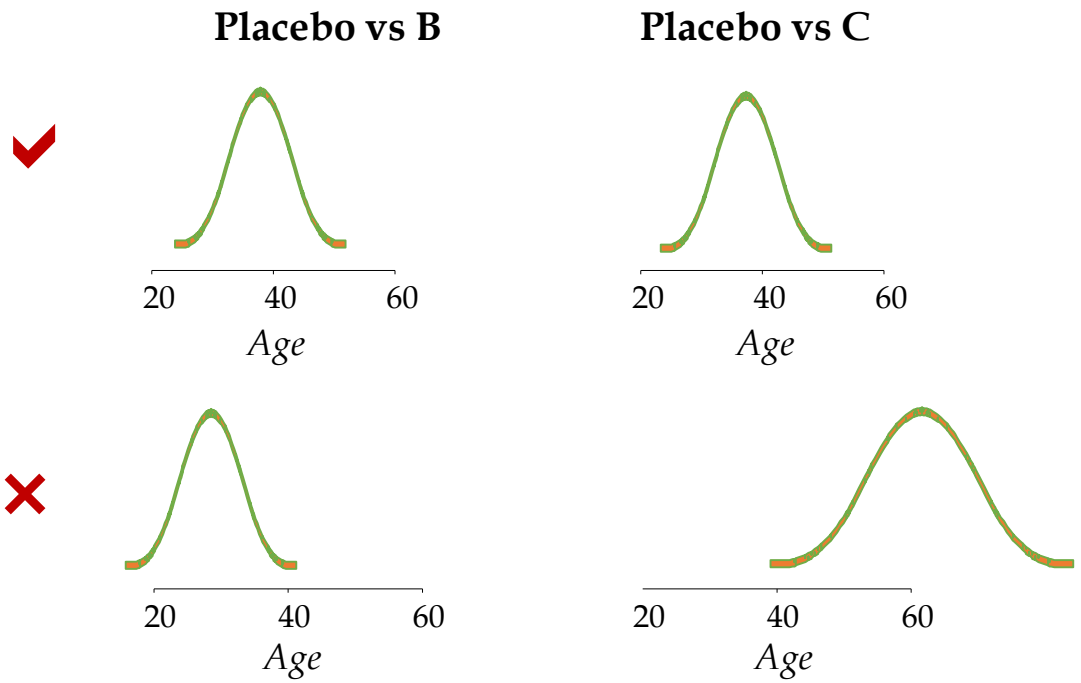
Transitivity at the protocol stage

- Consider whether 'missing' arms are likely missing at random
  - AC trials do not have B arms and AB trials do not have treatment C
  - Is this reasonable? In some clinical areas patients would never receive alternative treatments
    - e.g. Sequencing of drugs

- Consider if all treatments are "jointly randomizable"
  - The treatments need to be genuinely competing alternatives
  - It should possible to imagine a randomized trial comparing all treatments in the network
  - Could patients have been randomly allocated to any of the treatments?
    - e.g. first- and second-line chemotherapy regimens

Transitivity at the protocol stage

- Consider the distribution of possible effect modifiers of the relative treatment effects in AC and AB trials
  - identify a priori potential effect modifiers and compare how they are distributed across comparisons (see data extraction)
    - e.g. patients, trial protocols, doses, administration, etc. should be similar in ways which might modify the treatment effect



What to keep in mind for the eligible interventions

- Restricting your review to compare few interventions
  - limits its usefulness and applicability
  - you must justify your choice
  - risk to have unconnected networks
  - few data, low power (depends on the setting)
- Expanding the database too much to include many treatments
  - jeopardizes the transitivity assumptions (or at least makes its defense challenging)
  - renders review process long and data management difficult
- **Watch out for:** old and new treatments, ad-on treatments, intransitive legacy treatments
- *What will you do if you identify new interventions while scanning the literature?*
- *How to deal with different doses or drug class and co-interventions?*
  - Merging versus splitting

Thinking about transitivity

At the outset	Looking at the studies	Analysing the data
The treatments we compare are *in principle* jointly randomizable	The groups of studies that compare them do not differ with respect to the distribution of effect modifiers	Direct and indirect treatment effects are in statistical agreement
They have the same indication, we can imagine a mega-trial with all treatments being compared etc	Can be tested with enough studies per comparison	Various statistical tests if there is both direct and indirect evidence

Cipriani et al. ***Ann Int Med*** *2013*

Searching, selecting studies and extracting data

- Any study comparing at least two of the eligible interventions should be considered
  - i.e. all available direct comparisons between the eligible interventions should be included

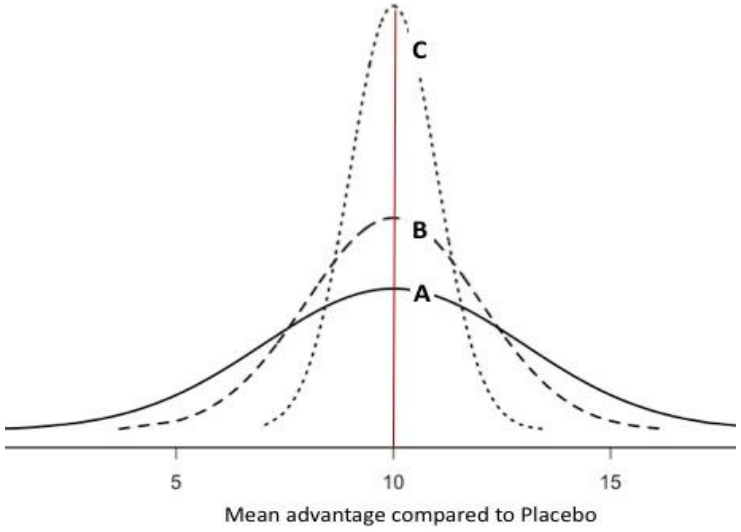
- Describe you will extract data on
  - **Outcomes:** study-level or arm-level preferable?
  - **Potential effect modifiers:**
    - population and study characteristics that may act as effect modifiers selected based on bibliography and clinical understanding
    - required to evaluate statistically the transitivity assumption and clinical/methodological heterogeneity
    - used also in additional analyses to explain statistical heterogeneity/incoherence
  - Risk of bias data, etc.

Selecting effect measures

- Usual considerations between OR/RR/RD or MD/SMD

- State which **measure will be used to rank the treatments** (if an objective of the review)
  - Avoid probability of being the best
  - Use SUCRAs/P-scores/mean ranks instead

    (Salanti et al. JCE 2011, Rucker et al. BMC Med Res Methodol 2015)



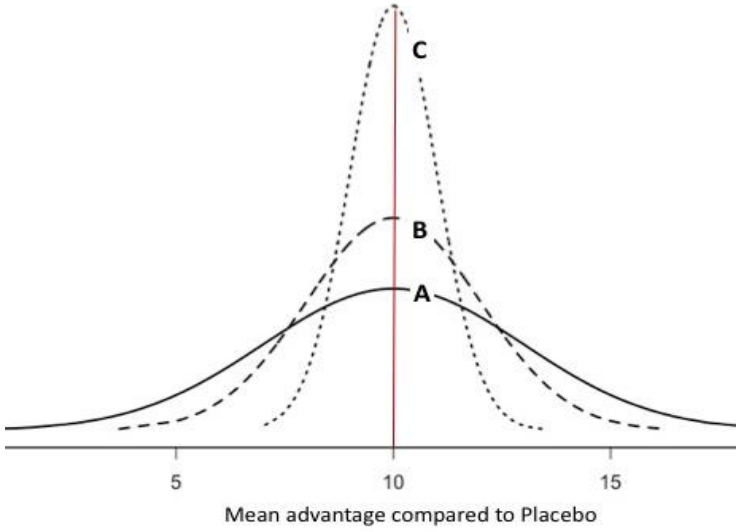
Treatment	Prob of being best
A	40%
B	33%
C	27%

Selecting effect measures

- Usual considerations between OR/RR/RD or MD/SMD

- State which **measure will be used to rank the treatments** (if an objective of the review)
  - Avoid probability of being the best
  - Use SUCRAs/P-scores/mean ranks instead

  (Salanti et al. JCE 2011, Rucker et al. BMC Med Res Methodol 2015)



Treatment	Prob of being best	SUCRA/ P-score	Mean Rank
A	40%	67%	2
B	33%	67%	2
C	27%	67%	2

Treatments with large uncertainty can be favoured by P(best)!

Cautious note about ranking

- Ranking measures are not substitutes for relative effect estimates
- Ranking based on SUCRAs or mean ranks accounts better for the uncertainty in relative ranking
  - Using P(best) to rank treatments can be misleading
- Ranking measures are conditional on the set of treatments being compared
  - SUCRAs and mean ranks will change when only a subset of interventions are compared
- Avoid ranking when there is a lot of uncertainty in the effect estimates or when there are important differences in the uncertainty across comparisons
- Methods that allow more information in ranking are available

(see for example Chaimani et al. PlosOne 2013, Salanti et al. PlonOne 2014, Choi et al 2019, Mavridis et al. Biometrical J 2019, Chaimani et al. MedRxiv 2019)

Evaluating transitivity

- Describe how you will evaluate the clinical and methodological comparability of studies (**heterogeneity**)
  - as in standard meta-analysis

- Describe how you will evaluate the plausibility of the **transitivity assumption**
  - the comparability/similarity of studies evaluating *different* comparisons
  - we can compare the distribution of effect modifiers across sets of studies grouped by comparison
  - in practice this is often difficult – be prepared and remember lack of evidence is not evidence of lack

Evaluating transitivity

- Example: psychological interventions for bipolar disorder

"To infer about the assumption of transitivity:
1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; for example, whether interventions are administered the same way in studies comparing active treatments to usual care (or no treatment) and in those comparing active treatments to other active treatments.
2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons (see 'Data extraction and management' for the list of potential effect modifiers). If the distributions are balanced across comparisons we will conclude against evidence of intransitivity."

(not against intransitivity!)

Cipriani et al. PROSPERO 2015:CRD42015016085

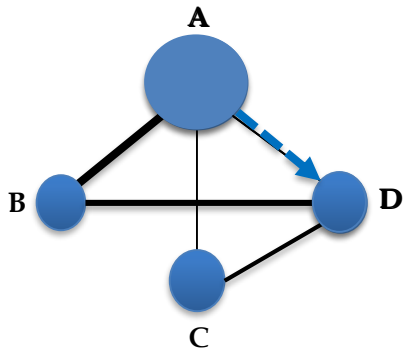
Describing the statistical analysis

- **Two possible types of analyses**:
  - A series of independent pairwise meta-analyses (usually as the first step of NMA)
  - Network meta-analysis
  - State whether both types of analyses will be performed
    - if the required assumptions are plausible
- Describe the **statistical model**
  - Bayesian or frequentist setting
  - fixed or random effects
  - common or different heterogeneity across the comparisons
- Report the **modelling details** (e.g method for heterogeneity, prior distributions)
- Explain how you will **handle variability in treatment definition** (e.g. different doses or modalities)
  - Analyze as separate treatment modes nodes
  - Model explicitly their variability
  - Additive/multiplicative models for complex interventions?
- Report the **software** of the analysis
  - e.g. STATA, R, BUGS
  - give the codes

Evaluating incoherence

Report on methods for:

- Assessment of **incoherence <u>locally</u>**
  - identify pairwise comparisons or loops of evidence that might be important sources of incoherence
  - e.g. node-splitting approach



$$\mu^{dir} - \mu^{ind} = IF$$

…using information from the entire network

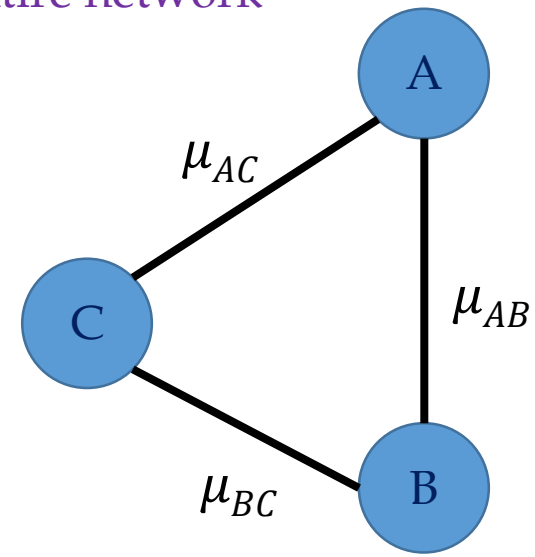
Evaluating incoherence

Report on methods for:

- Assessment of **incoherence <u>locally</u>**
  - identify pairwise comparisons or loops of evidence that might be important sources of incoherence
  - e.g. node-splitting approach

- Assessment of **incoherence <u>globally</u>**
  - evaluate the presence of incoherence in the entire network
  - e.g. design-by-treatment interaction model
  - Compare coherence vs incoherence models

The coherence model



coherence equation

$$\mu_{BC} = \mu_{AC} - \mu_{AB}$$

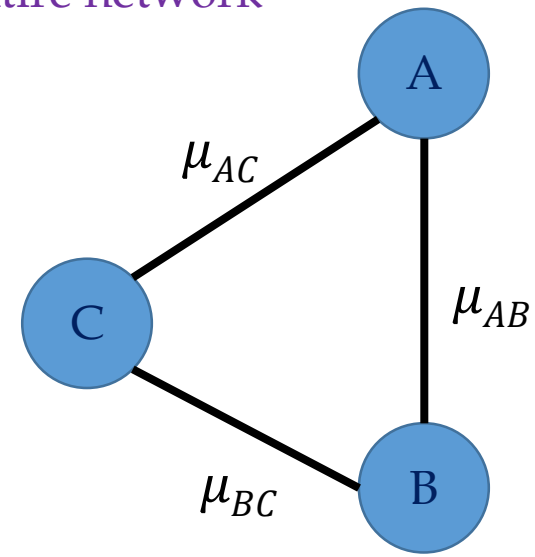
Evaluating incoherence

Report on methods for:

- Assessment of **incoherence <u>locally</u>**
  - identify pairwise comparisons or loops of evidence that might be important sources of incoherence
  - e.g. node-splitting approach

- Assessment of **incoherence <u>globally</u>**
  - evaluate the presence of incoherence in the entire network
  - e.g. design-by-treatment interaction model
  - Compare coherence vs incoherence models

The incoherence model



coherence equation

$$\mu_{BC} = \mu_{AC} - \mu_{AB} + w_{ABC}$$

Investigating heterogeneity and incoherence

- Heterogeneity & incoherence → caused by differences in populations and study characteristics **within** and **across** comparisons

- Specify the **additional analyses** that will be performed to explain heterogeneity and inconsistency
  - e.g. **subgroup analyses, network meta-regression** (if sufficient data are available)

- **Pre-specify the variables** that will be considered as possible sources of heterogeneity and incoherence
  - choose a subset of the potential effect modifiers listed earlier (see also Data Extraction)

Reporting bias and small-study effects

- It is as much of a threat as in pairwise meta-analysis
- Use **contour-enhanced funnel plots** (per comparison)

Peters et al. JCE 2008;61(10):991-6

- Use **comparison-adjusted funnel plots** (for the entire network)

Chaimani et al PlosOne 2013

- Use **network meta-regression models**

Chaimani and Salanti ResSynthMeth 2012

Require assumptions about the direction of potential small study effects!

- Judge how comprehensive was the literature search and whether unpublished studies have been identified
- Use **selection models** in the case of serious reporting bias

Mavridis et al. Stat Med. 2014;33(30):5399-412

Evaluating confidence in the evidence

BMJ 2014;349:g5630 doi: 10.1136/bmj.g5630 (Published 24 September 2014)

RESEARCH METHOD

A GRADE Working Group appro quality of treatment effect estima meta-analysis

Network meta-analysis (NMA), combining direct and indirec
used to examine the comparative effectiveness of medical i
on how to rate the quality of evidence supporting treatment
We present a four-step approach to rate the quality of evide
NMA estimates based on methods developed by the GRAD
a published NMA, we show that the quality of evidence supp
to very low across comparisons, and that quality ratings give
and likely to mislead.

Milo A Puhan [1], Holger J Schünemann [2], Mohammad Hassa
Brignardello-Petersen [5], Jasvinder A Singh [6], Alfons G Kesse
Working Group

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

HOME | ABOU

Search

New Results

Comment on this paper

Assessing Confidence in the Results of Network Meta-Analysis (Cinema)

Adriani Nikolakopoulou, Julian PT Higgins, Theodore Papakonstantinou, Anna Chaimani, Cinzia Del Giovane, Matthias Egger, Georgia Salanti

doi: https://doi.org/10.1101/597047

This article is a preprint and has not been peer-reviewed [what does this mean?].

Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

Network meta-analysis in Cochrane

- 104 Cochrane reviews and 50 protocols have NMA in the title, abstract, or keyword as of October 16, 2019

- Examples of recently published NMAs
  - Antibiotic treatment for spontaneous bacterial peritonitis in people with decompensated liver cirrhosis: a network meta-analysis
  - Interventions for maintenance of surgically induced remission in Crohn's disease: a network meta-analysis
  - Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis
  - Interventions for unexplained infertility: a systematic review and network meta-analysis
  - Pharmacological interventions for the treatment of delirium in critically ill adults

Comparing Multiple Interventions Methods Group

- Registered in October 2010; with a little over 100 members in Archie
- Covers methodology of (1) NMA and (2) overviews of reviews
- Current co-covenors:

Deborah Caldwell
University of Bristol, UK

Anna Chaimani
Paris Descartes University, France

Tianjing Li
University of Colorado Anschutz Medical Campus, USA

Lisa Hartling
University of Alberta, Canada

Training events

- We strongly recommend that all reviews include NMAs have a statistician in the review team
- Numerous workshops at Cochrane Colloquia
- Upcoming short courses
  - 3-day NMA course in Paris: From planning to publication (4-6 December 2019, registration deadline 20 November 2019) (http://livenetworkmetaanalysis.com/nma-training/)
  - 2-day course at University of Bristol (11-12 December) (https://www.epi-winterschool.org)
  - 3-day course at Swiss Epidemiology Winterschool (January 2020) (https://www.epi-winterschool.org)
  - 2-day course at EPIsummer of Columbia University (June 2020) (https://www.mailman.columbia.edu/research/episummercolumbia)