Quesito Clinico e confronti indiretti

Giovanni L. Pappagallo

G.L. Pappagallo: relazioni con l'Industria farmaceutica e potenziali conflitti di interesse (10.2017)

Azienda	Relazione	Patologia
Sanofi	training, valutazioni clinico-epidemiologiche	ca. prostata, m. diabetica, m. cardiovascolari, sclerosi multipla
Janssen	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. prostata
Takeda	training, partecipazione advisory board	ca. prostata, ca.mammella
Astellas	training, partecipazione advisory board	ca. prostata
Pfizer	training, valutazioni clinico-epidemiologiche	aa. mammario, ca. rene, artrite reumatoide, m. cardiovascolari
IPSEN	valutazioni clinico-epidemiologiche	ca. rene
Roche	training, valutazioni clinico-epidemiologiche	ca. polmone, ca. ovaio, sclerosi multipla, linfomi, ACG
Novartis	training	ca. rene, ca. mammella
UCB	training, valutazioni clinico-epidemiologiche	m. di Parkinson, m. epilettica, artrite reumatoide, artrite psoriasica, spondilite anchilosante
Pierre Fabre	training	ca. vescica

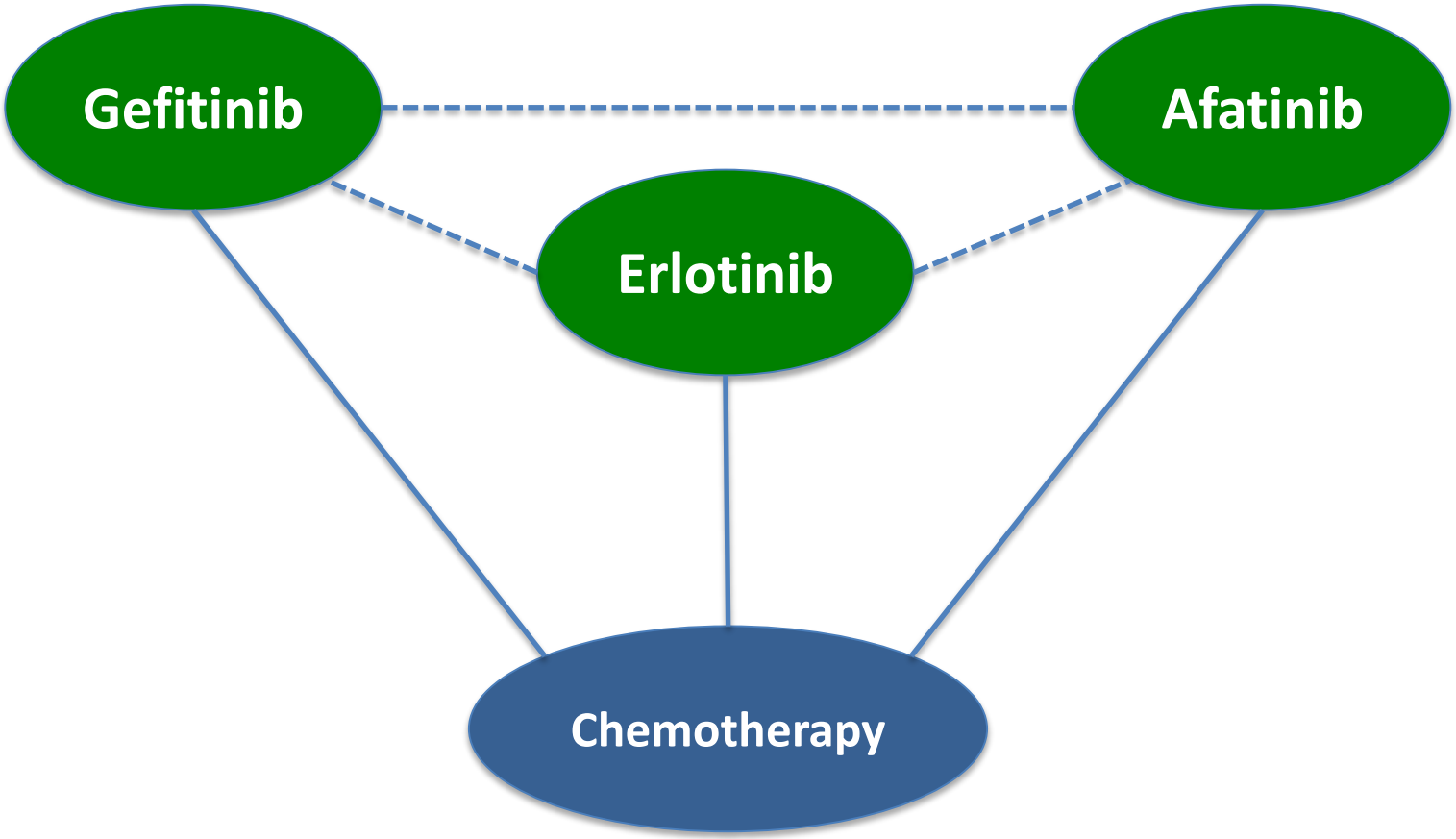
Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.

Unmet medical need
ma assenza di confronti diretti…



Defining the review question

A clearly defined, focused review begins with a well framed question.

The review question should specify:

- types of **population** (participants),
- types of **interventions** (and comparisons),
- types of **outcomes** that are of interest.

*These components of the question, with the additional specification of **types of study** that will be included, form the basis of the pre-specified eligibility criteria for the review.*

Comparative evaluation of group-based mindfulness-based stress reduction and cognitive behavioral therapy for the treatment and management of chronic pain disorders: protocol for a systematic review and meta-analysis with indirect comparisons

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Systematic Reviews 2014, **3**:134

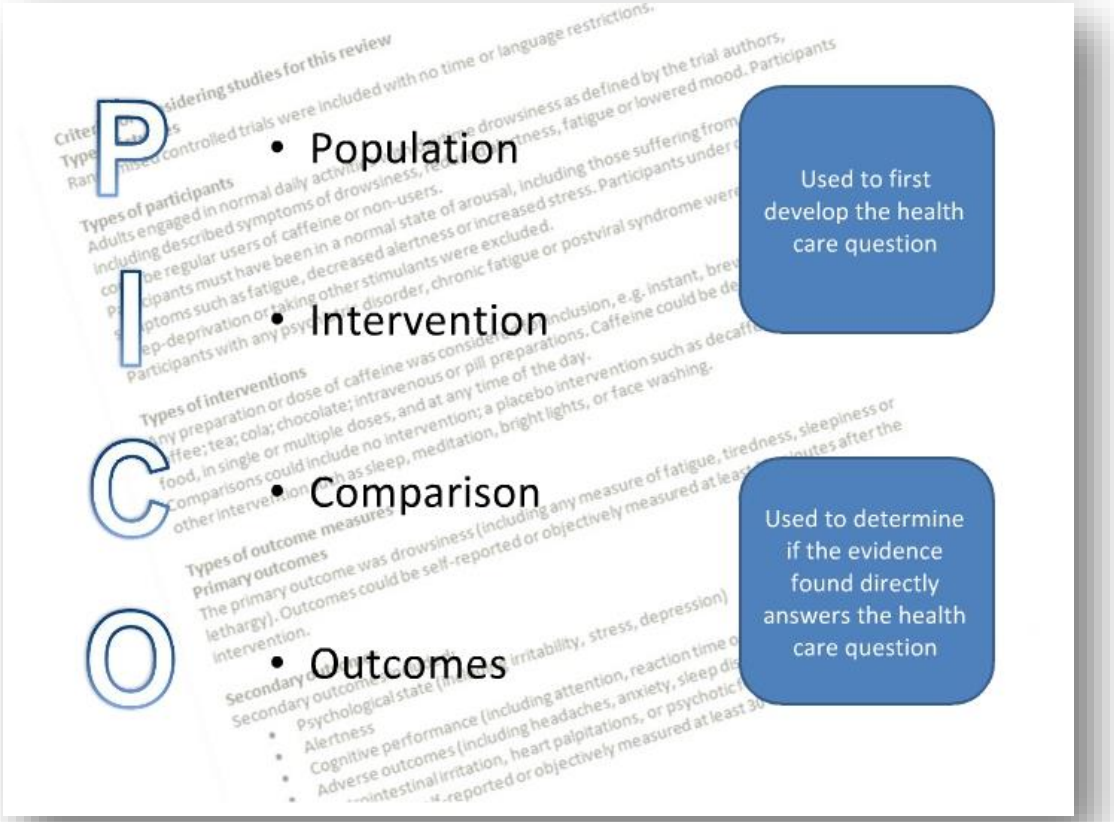
We are not aware of any existing studies comparing CBT and MBSR directly, and thus, evidence synthesis methods enabling indirect comparisons between interventions are likely to be helpful.

Type of studies

We will include randomized controlled trials that have evaluated the efficacy of MBSR or CBT programs for any chronic pain disorder. This will include treatment groups compared with standard care, treatment groups compared with wait-list/no-treatment conditions, and treatment groups with adjunctive treatments compared with the same adjunctive treatments alone.

The ‘clinical question’ should specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.

The acronym PICO (**P**articipants, **I**nterventions, **C**omparisons and **O**utcomes) helps to serve as a reminder of these.



Which Populations?

The criteria for considering types of people included in studies in a review should be **sufficiently broad** to encompass the likely diversity of studies, **but sufficiently narrow** to ensure that a meaningful answer can be obtained when studies are considered in aggregate.

It is often helpful to define the types of people that are of interest in two steps:

- ✓ diseases or conditions of interest using explicit criteria for establishing their presence or not;
- ✓ the broad population and setting of interest

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Type of participants

We will include studies of all adults (i.e., ≥18 years old) with chronic pain conditions in both treatment and control participants. We will adopt the definition of pain provided by the International Association for the Study of Pain.

Which comparisons to make?

The second key component of a well-formulated question is to specify the **interventions of interest and the interventions against** which these will be compared (comparisons).

- ✓ *Consider exactly what is delivered, at what intensity, how often it is delivered, who delivers it, etc.*
- ✓ *Are the interventions to be compared with an inactive control intervention (e.g. placebo, no treatment), or with an active control intervention (e.g. a different variant of the same intervention, a different drug, a different kind of therapy)?*

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Type of interventions

Eligible MBSR programs must adhere to the standardized program format developed by Kabat-Zinn. Eligible CBT programs must be delivered in group, in-person formats.

Eligible interventions will also include standard care groups and wait-list/no-treatment conditions given the anticipated need for indirect comparison methods to compare MBSR with CBT.

Which outcome measures are most important?

The third key component of a well-formulated question is the delineation of particular **outcomes** that are **of interest**.

Outcomes

Should be
importance driven
NOT
evidence driven

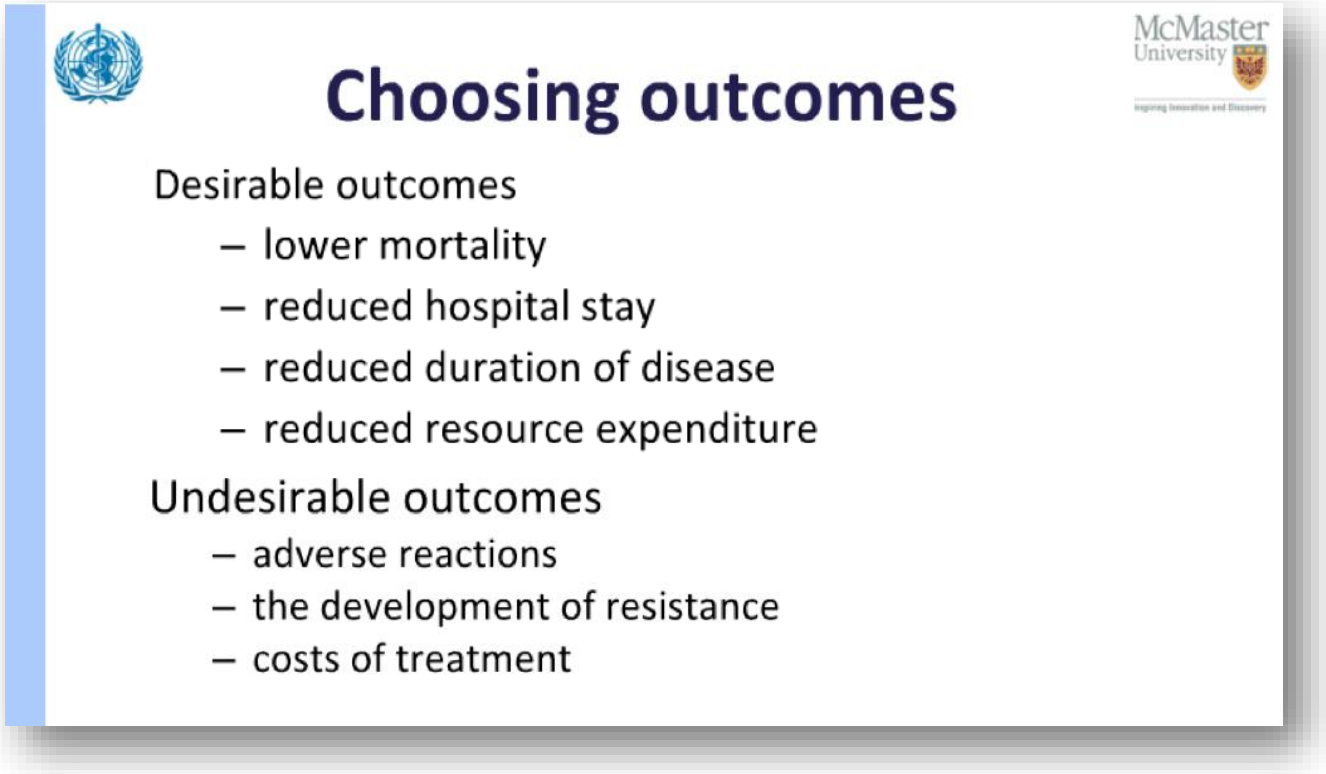
Which outcome measures are most important?

The third key component of a well-formulated question is the delineation of particular outcomes that are of interest.

- ✓ *Outcomes considered to be meaningful, and therefore addressed in a review, will not necessarily have been reported in individual studies.*
- ✓ *Including all important outcomes in a review will highlight gaps in the primary research and encourage researchers to address these gaps in future studies.*

Which outcome measures are most important?

It is critical that outcomes used to assess adverse effects as well as outcomes used to assess beneficial effects are among those addressed by a review



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Type of outcome measures

We are primarily interested in outcomes that measure change in pain interference from pre to post MBSR or CBT treatment as an index of improvement in patients' physical functioning.

Secondary outcomes of interest include pain intensity, emotional functioning, and patients' global impression of change.

These variables are commonly measured using psychometric tools with demonstrated reliability and validity. This includes …

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Clinical Epidemiology 2013:5 173–183

Potential sources of discordance
Clinical question (PICO) – are the clinical questions similar? • Patient population (P) – are the defined patient populations similar? • Interventions (I) – are the interventions similar? • Controls (C) – are the control interventions similar? • Outcomes (O) – are the chosen outcomes similar?
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Indirect and multiple treatment comparisons

	Cooper et al[22]	Cooper et al[21]	Cure et al[23]	Kieran et al[24]
Clinical question (PICO)				
Are the defined patient populations similar?	Adult patients with chronic hepatitis C genotype 1 infection	Adult patients with chronic hepatitis C genotype 1 infection	Adult patients with chronic hepatitis C genotype 1 infection	Adult patients with chronic hepatitis C genotype 1 infection
Are the interventions similar? Are the control interventions similar?	• Boceprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin • Telaprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin	• Boceprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin • Telaprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin • Peginterferon alpha-2a + ribavirin versus peginterferon alpha-2b + ribavirin	• Boceprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin • Telaprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin • Peginterferon alpha-2a + ribavirin versus peginterferon alpha-2b + ribavirin	• Boceprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin • Telaprevir + peginterferon alpha + ribavirin versus peginterferon alpha + ribavirin
Are the chosen outcomes similar?	Primary outcome: Sustained virologic response	Primary outcome: Sustained virologic response	Primary outcome: Sustained virologic response	Primary outcome: Sustained virologic response

Each of the four reports assessed adult patients with chronic hepatitis C genotype 1 infection

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Are the chosen outcomes similar?	Primary outcome: Sustained virologic response	Primary outcome: Sustained virologic response	Primary outcome: Sustained virologic response	Primary outcome: Sustained virologic response

The considered interventions were boceprevir or telaprevir in combination with standard of care (peginterferon alpha plus ribavirin) versus standard of care alone.

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In reports by Cooper et al and Kieran et al, peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin were considered to have equivalent treatment effects, and therefore were not evaluated separately in the analyses.

In contrast, these two interventions were considered as separate in reports by Cooper et al and Cure et al.

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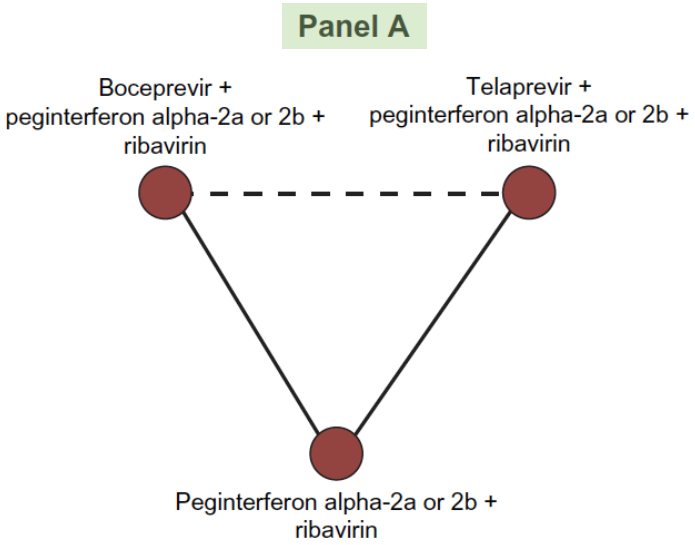

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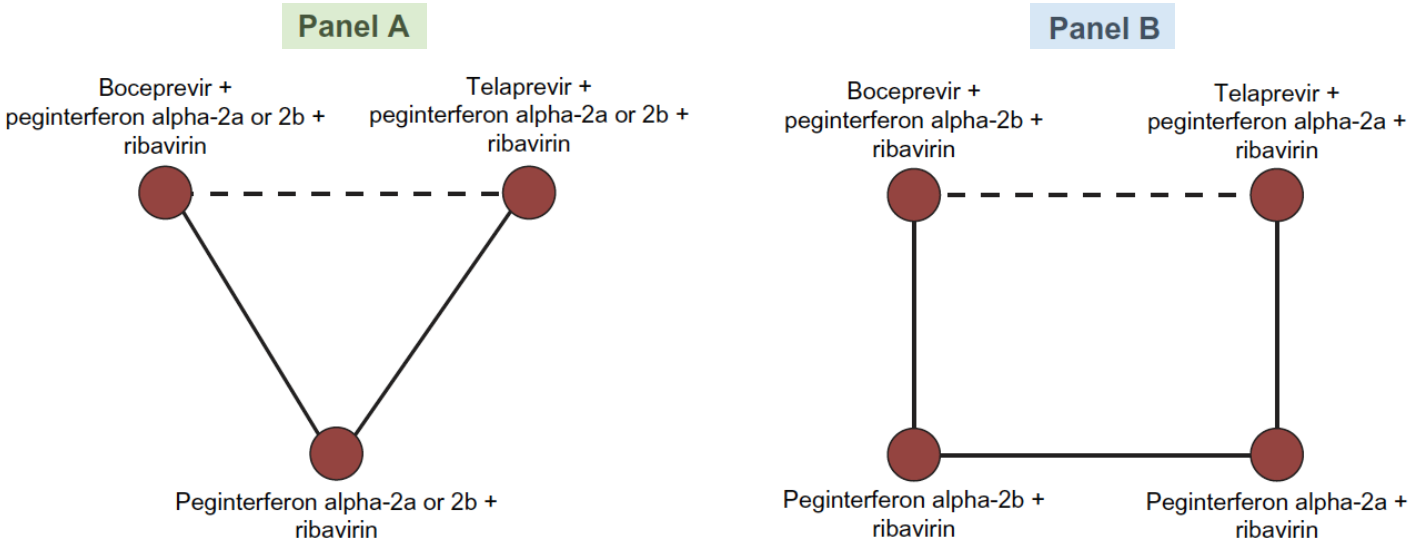

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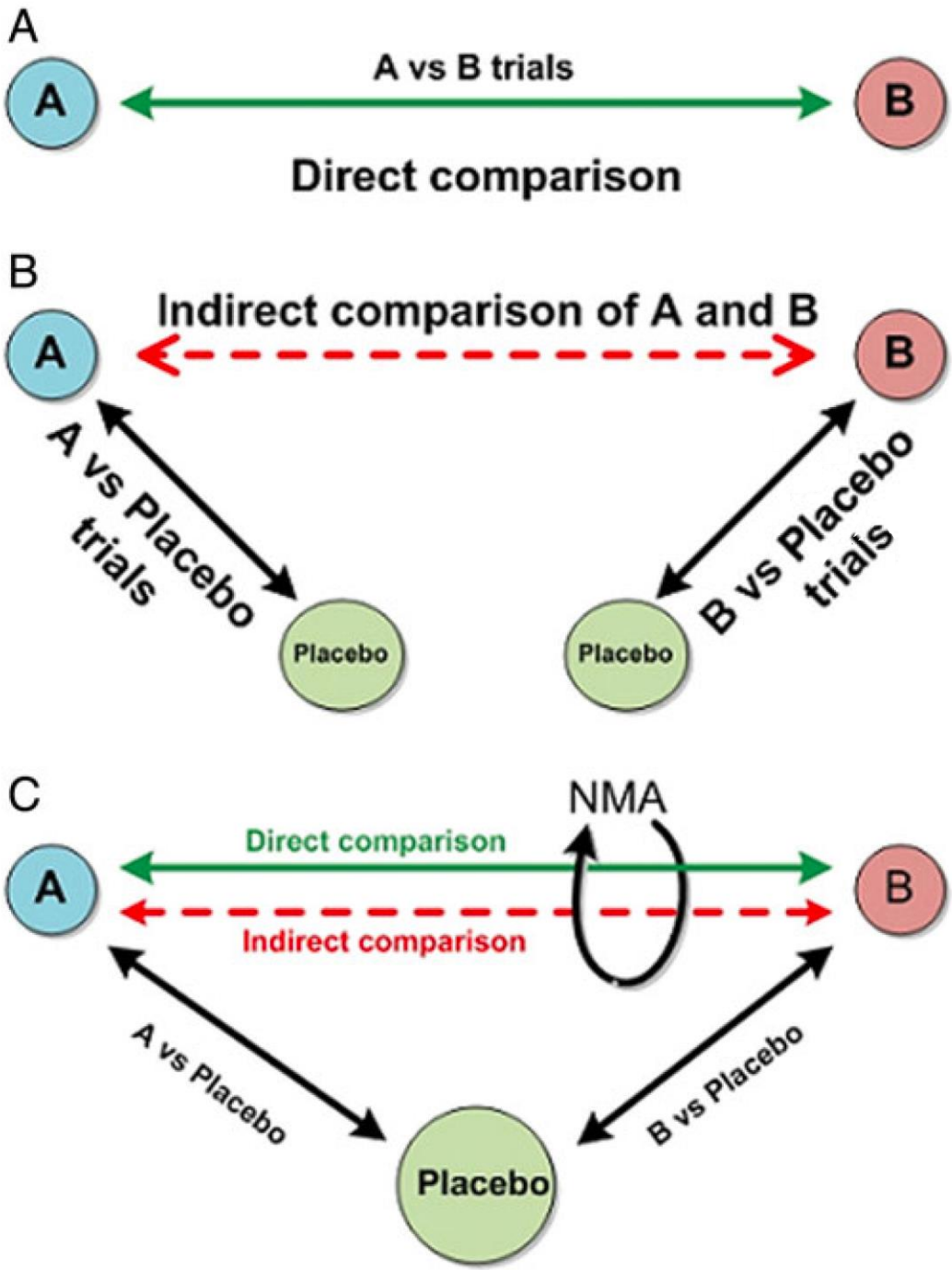
SVR was consistently defined as an undetectable level of hepatitis C virus ribonucleic acid (HCV-RNA) at the end of the 24-week posttherapy follow-up period. HCV-RNA was measured using the COBAS TaqMan HCV-RNA assay in all the RCTs assessing boceprevir and telaprevir that were included in the ITC and MTC analyses.

What is indirect comparison?

Fujian Song
BMed MMed PhD
Reader in Research Synthesis, Faculty of Health, University of East Anglia

Basic assumptions underlying indirect comparisons include a **homogeneity assumption** for standard meta-analysis, **similarity assumption** for adjusted indirect comparison and **consistency assumption** for the combination of direct and indirect evidence. It is essential to fully understand and appreciate these basic assumptions in order to use adjusted indirect and mixed treatment comparisons appropriately.


A
A vs B trials
A
B
Direct comparison
B
Indirect comparison of A and B
A
B
A vs Placebo trials
B vs Placebo trials
Placebo
Placebo
C
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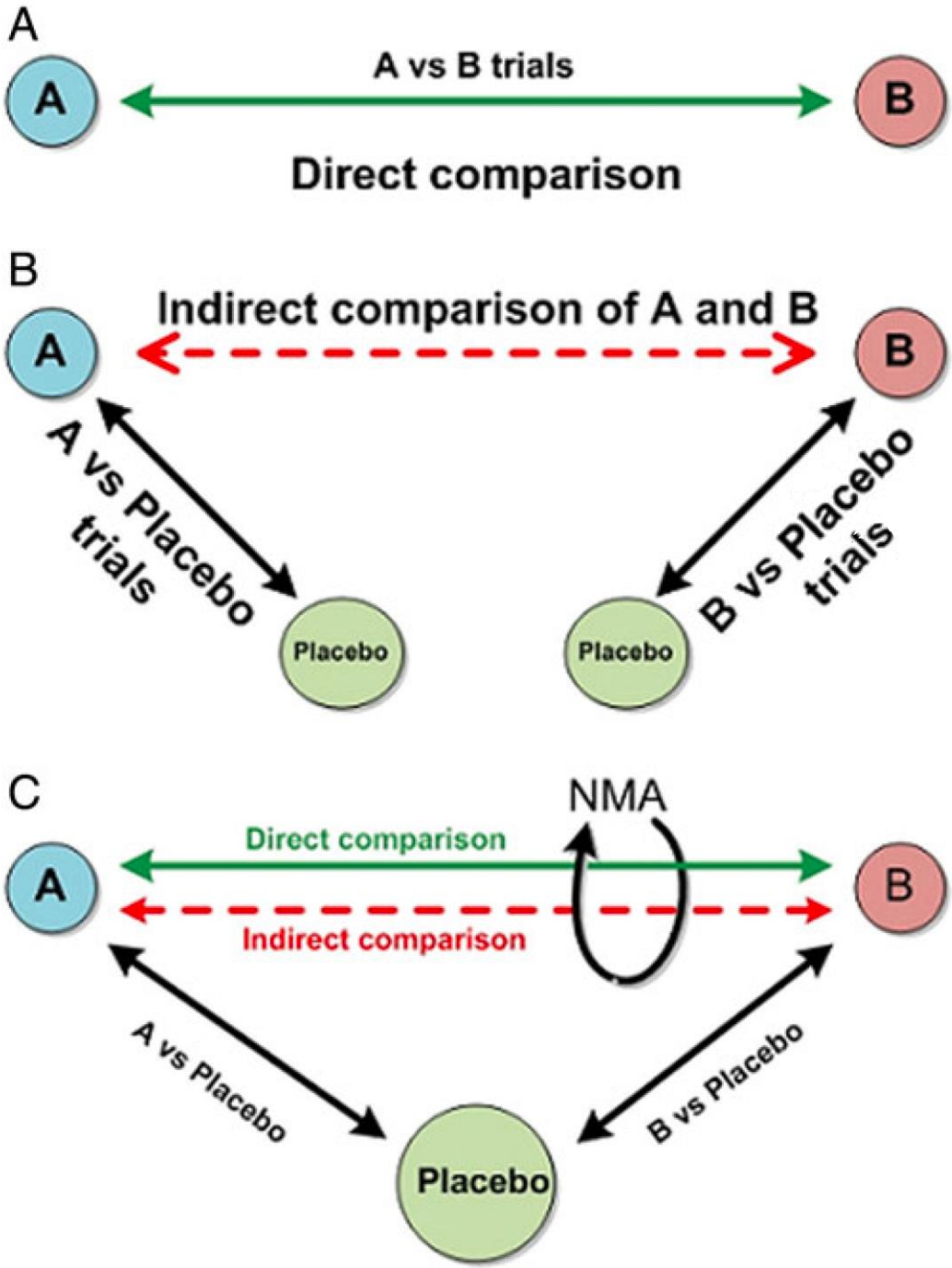
Placebo

Similarity



Similarity

Consistency