

Evidence based clinical pharmacy WK8



Phil Wiffen Editor in Chief EJHP

Conflict of interest

- No conflicts relevant to this presentation

Three questions !

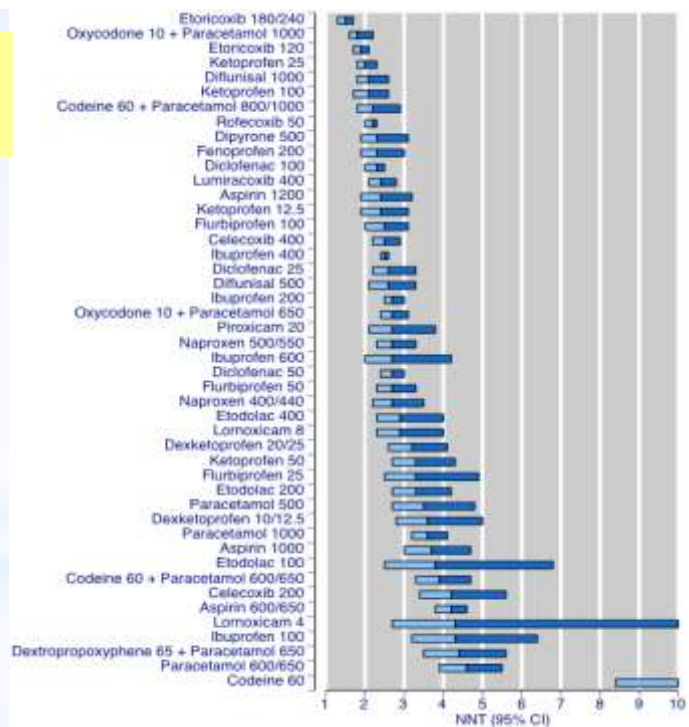
- **A forest plot is a means to present an average ?**
- **Large values for numbers needed to treat (NNTs) show a bigger effect than small ones?**
- **Systematic reviews are the most reliable evidence?**
- **Answer YES(green) or NO(red)**

The rationale

- **Evidence based medicine**
- **What is evidence ?**
- **What are systematic reviews ?**
- **Tools to present data**

Reliable evidence in acute pain from the Cochrane Pain Group

NNT for at least 50% maximum pain relief over 4-6 hours



What evidence-based medicine is:

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

Sackett (BMJ 1996; 312: 71-2)

What evidence-based medicine is:

The practice of EBM requires the integration of

- **individual clinical expertise**
with the
- **best available external clinical evidence from systematic research.**

Another definition of EBM

Evidence based medicine is an approach to health care that promotes the collection, interpretation and integration of valid, important and applicable patient reported, clinician observed and research derived evidence. The best available evidence, moderated by patient circumstances and preferences, is applied to improve the quality of clinical judgements.

McKibbin KA et al 'The medical literature as a resource for Evidence Based Care'
<http://hiru.mcmaster.ca/hiru/medline/mdl-ebc.htm>

“There are perhaps 30000 biomedical journals in the world, and they have grown steadily by 7% a year since the seventeenth century.

Yet about 15% of medical interventions are supported by solid scientific evidence...

...only 1% of the articles in medical journals are scientifically sound”

R. Smith quoting Prof. D. Eddy, BMJ
1991; 303: 798-99

“...approximately 17000 new biomedical books are published annually.”

Lowe and Barnett, JAMA
1994; 271: 1103-8

More than 25 000 RCTs have been published in pain relief research since 1950

The size of the task

How many biomedical papers are there ?

- Medline 21 million records, 5600 journals, 80 countries
- Embase 28 million records, 8400 journals, 70 countries
- CINAHL 4.2 million records 5400 journals. 13 languages
- Others: e.g. LILACS ????

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Tools not Rules

Type & Strength of Evidence

- I Strong evidence from at least 1 systematic review of multiple well-designed randomised controlled trials**
- II Strong evidence from at least 1 properly designed randomised controlled trial of appropriate size**
- III Evidence from well designed trials without randomisation, single group pre-post, cohort, time series or matched case-controlled studies**
- IV Evidence from well-designed non experimental studies from more than 1 centre or research group**
- V Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees**

What is a systematic review ?

- Filing Cabinets
- Friends
- Foreigners ?
- The world literature on a subject

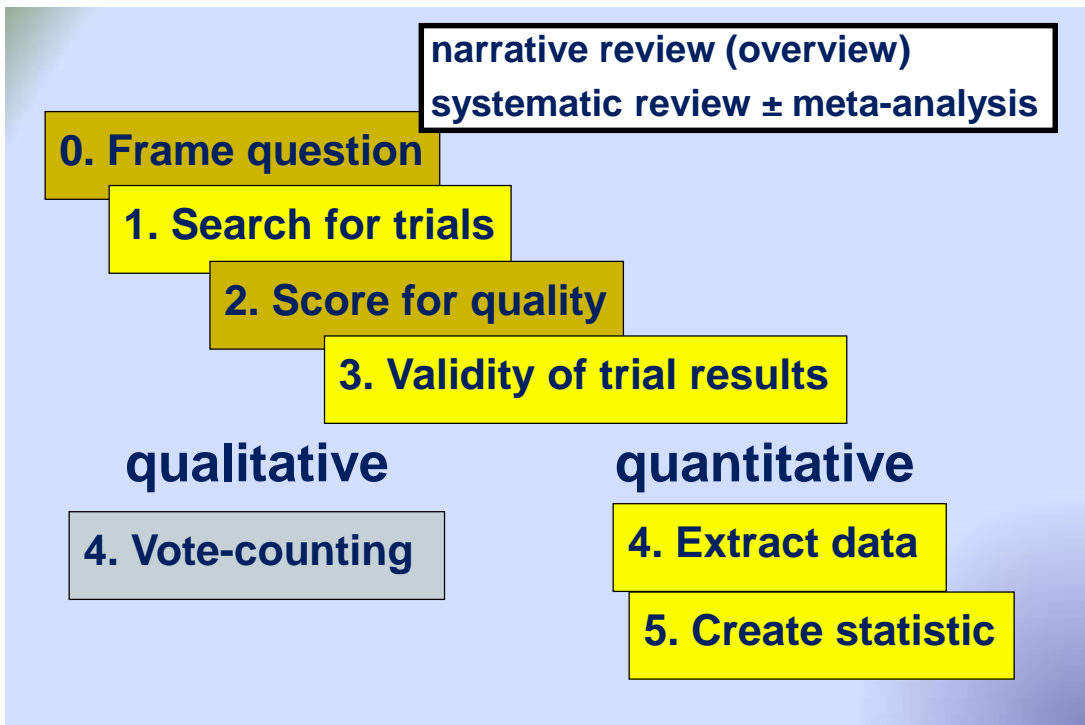
Systematic Reviews

“Clinical review articles should be as scientific as the articles they review”

Haynes, BMJ 1992; 304: 330-1

“ The fundamental difference between a review and a primary study is the unit of analysis, not the scientific principles that apply”

Oxman & Guyatt, CMAJ 1988; 138: 697-703



'Risk of bias' assessment in Cochrane reviews

☰ Risk of bias table

Item	Authors' judgment	Description
Adequate sequence generation?	Unclear	"Patients were randomly allocated"
Allocation concealment?	Unclear	No information.
Blinding?	Yes	"double blind design". "Millet... resembles lecithin in appearance... When ground, each substance could be distinguished from the other by hue and taste but staff were not informed as to which was which."
Incomplete outcome data addressed?	No	Data unavailable for meta-analysis. Randomised: lecithin = Not stated, placebo = Not stated, Total = 33. Missing: lecithin = 7 (non-cooperation or diarrhoea = 2; moved to nursing home = 4, death = 2), placebo = 5 (non-cooperation or diarrhoea = 3, death = 2), total missing = 36%.
Free of selective reporting?	No	No quantitative results reported due to lack of effect. It is apparently clear which outcomes were measured.
Free of other bias?	Yes	No problems apparent

Risk of bias summary

	Adequate sequence generation	Allocation concealment	Blinding (Patient-reported outcomes)	Blinding (Mortality)	Incomplete outcome data addressed (Short-term outcomes (< 6 wks))	Incomplete outcome data addressed (Longer-term outcomes (> 6 wks))	Free of selective reporting	Free of other bias
Barry 1988	+	-	+	+	-	-	-	-
Baylis 1989	+	+	+	+	?	?	+	?
Cooper 1987	+	?	-	?	-	-	+	?
Dodd 1985	+	?	+	+	+	-	?	?
Goodwin 1986	+	+	+	+	+	+	+	+
Sanders 1983	+	+	-	?	-	-	-	-

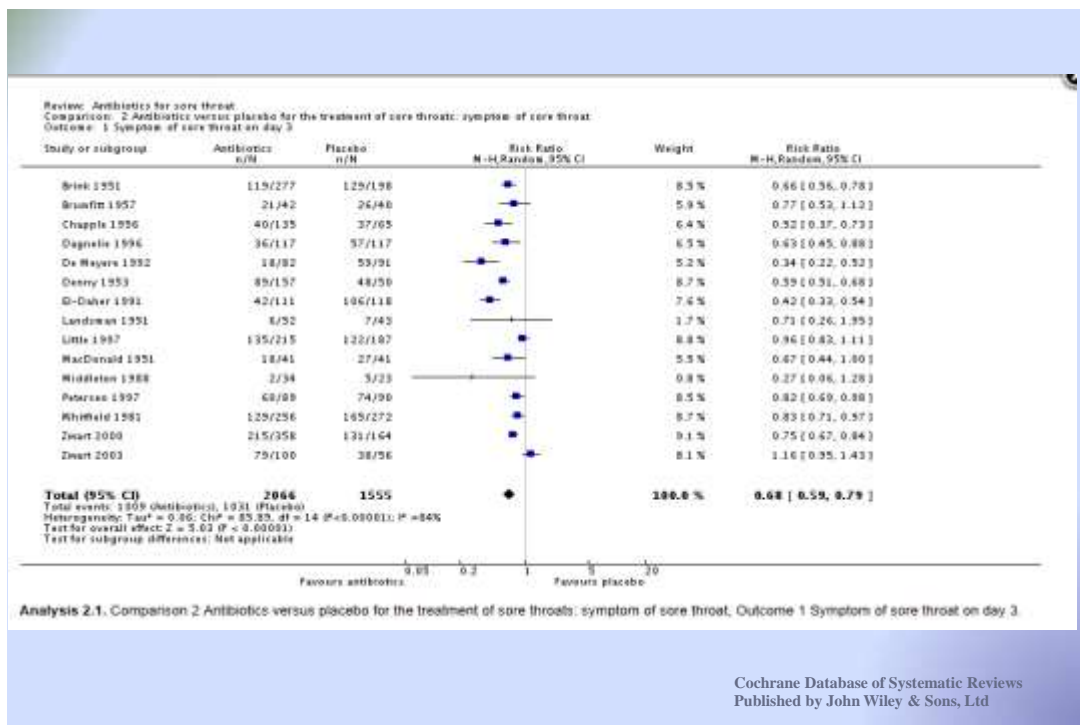
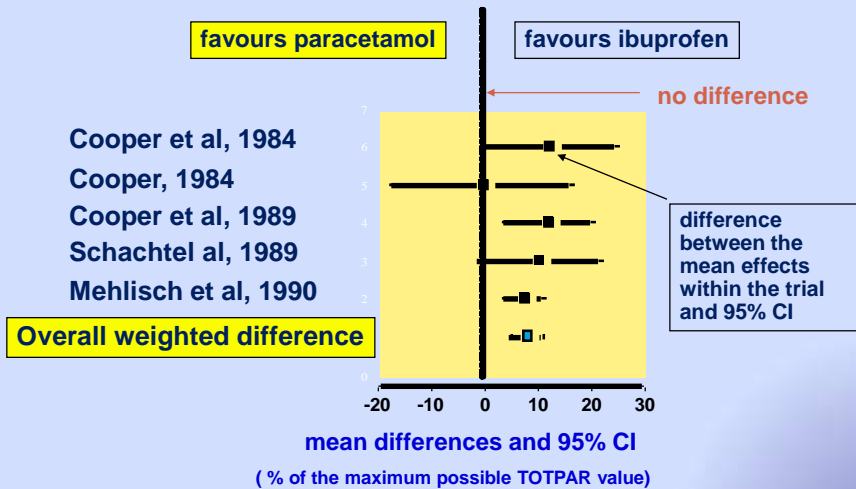
Tools to present data

Meta-analysis

NNTs

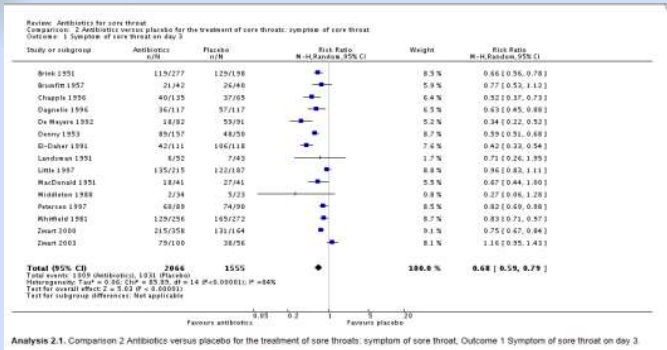
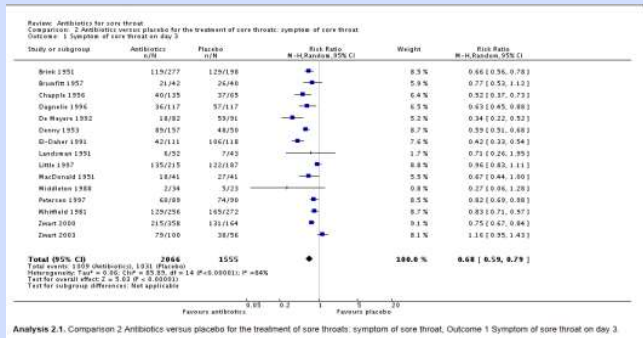
L'Abbé plots

Ibuprofen 400 mg vs. paracetamol 1000 mg for acute postoperative pain



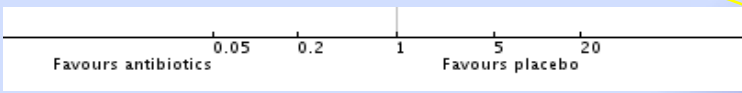
Review: Antibiotics for acute otitis media in children
Comparison: 1 Antibiotic versus placebo
Outcome: 1 Pain

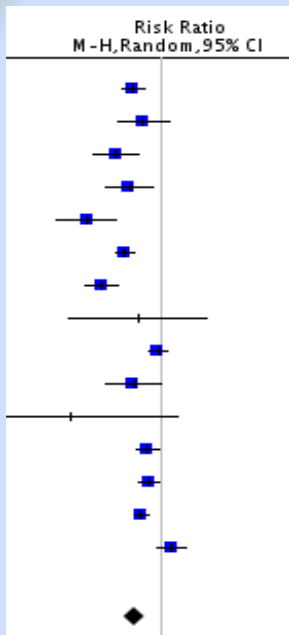
There is a label to tell you what the comparison is and what the outcome of interest is



At the bottom there's a horizontal line. This is the scale measuring the treatment effect. Here the outcome is

Take care to read what the labels say – things to the left do not always mean the treatment is better than the control.





The vertical line in the middle is where the treatment and control have the same effect – there is no difference between the two

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brink 1951	119/277	129/198	■	8.5 %	0.66 [0.56, 0.78]

For each study there is an ID

The data for each trial are here, divided into the treatment and control groups

This is the % weight given to this study in the pooled analysis

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brink 1951	119/277	129/198		8.5 %	0.66 [0.56, 0.78]

↑
The data shown in the graph are also given numerically

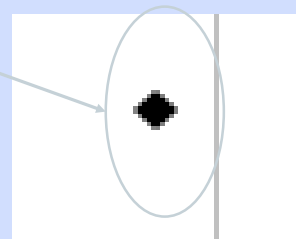


← The label above the graph tells you what statistic has been used

- Each study is given a blob, placed where the data measure the effect.
- The size of the blob is proportional to the % weight
- The horizontal line is called a confidence interval and is a measure of how we think the result of this study might vary with the play of chance.
- The wider the horizontal line is, the less confident we are of the observed effect.

Total (95% CI)	2066	1555		100.0 %	0.68 [0.59, 0.79]
<small>Total events: 1009 (Antibiotics), 1031 (Placebo) Heterogeneity: Tau² = 0.06; Chi² = 85.89, df = 14 (P < 0.00001); I² = 84% Test for overall effect: Z = 5.03 (P < 0.00001) Test for subgroup differences: Not applicable</small>					

The pooled analysis is given a diamond shape where the widest bit in the middle is located at the calculated best guess (point estimate), and the horizontal width is the confidence interval



**** Note on interpretation ****

If the confidence interval crosses the line of no effect, this is equivalent to saying that we have found no statistically significant difference in the effects of the two interventions

Numbers needed to treat (NNTs)

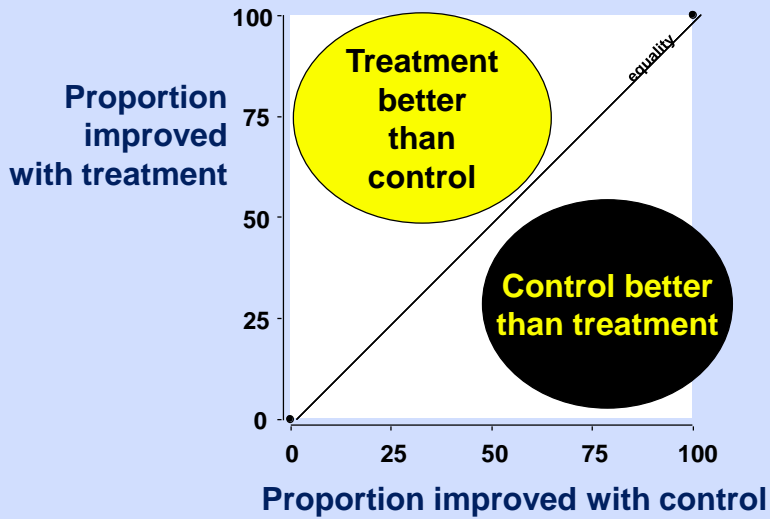
The Number of people who have to be treated for ONE to benefit

Number-needed-to-treat (NNT)

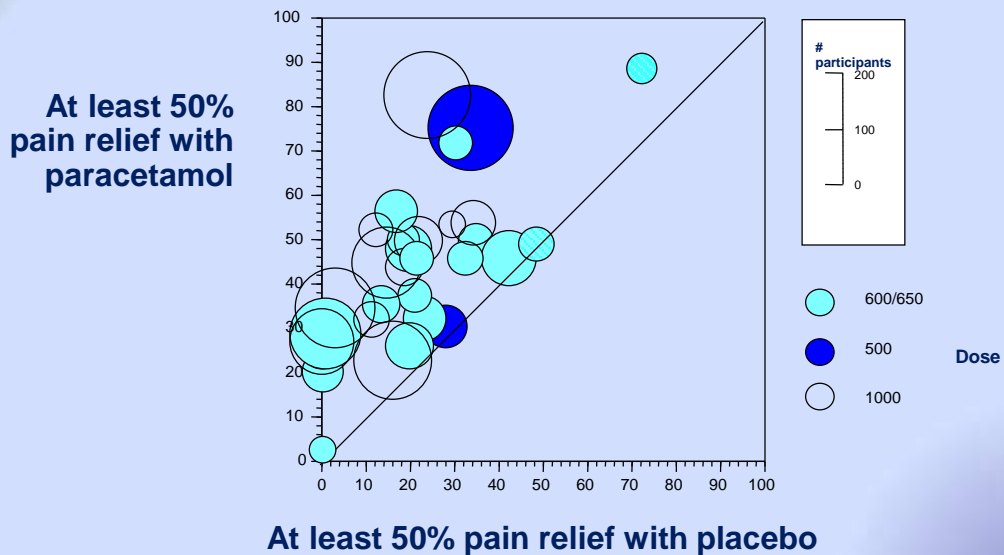
	Controls	Actives
Number of patients Improved = Clinical end point	N_{con} Imp_{con}	N_{act} Imp_{act}

$$NNT = \frac{1}{\frac{Imp_{act}}{N_{act}} - \frac{Imp_{con}}{N_{con}}}$$

L'Abbé plot for treatment



Paracetamol in acute pain –single dose



Moore et al Pain 1997;70:193

Other types of reviews

Rapid reviews
Overviews
Network Meta-analysis

Rapid reviews

- **Streamlined approach to evidence synthesis- often new technologies**
- **Follows standard SR route**
- **Uses hierarchy of evidence looking for SRs, if none then other sources, RCTs, quasi –experimental, other.**
- **Limited or cautious interpretation of findings**
- **Time frame of around 5-6 weeks**

Khangura et al. Systematic Reviews 2012,1:10

Rapid reviews-to think about

- **Seen by some as a cheap solution**
- **Can be misleading if key evidence missed**
- **Can always carry out a SR rapidly by using lots of resource**
- **Concept is poorly defined and understood**

Overviews of reviews

- **Too much evidence is rapidly becoming too many systematic reviews!**
- **Aim to describe a number of SRs in one overview to aid clinical decision making**
- **Cochrane is developing this and NIHR are encouraging development.**
- **Lots of discussion around methods and interpretation- particularly indirect comparisons**

Overview results table

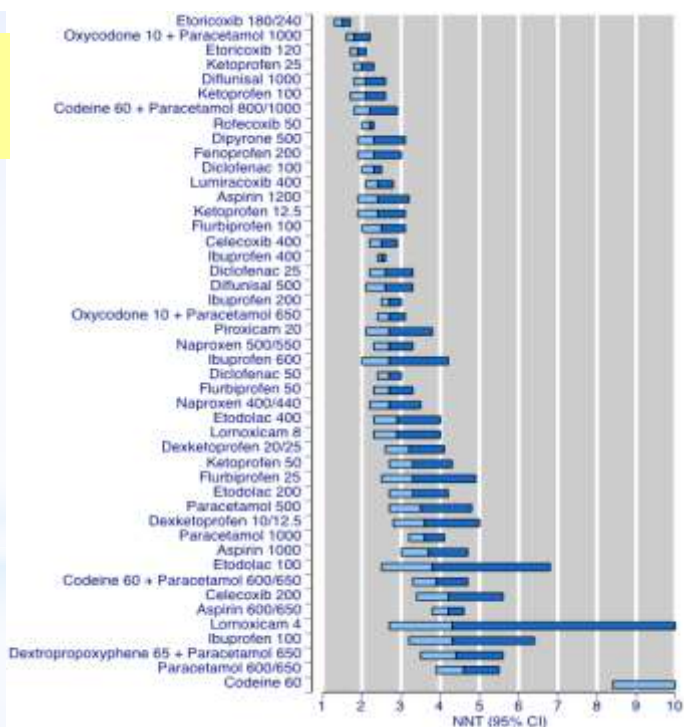
Summary of results C: Postherpetic neuralgia - efficacy analyses for different outcomes

Drug	Dose (mg/day)	Number of		Percent achieving outcome with		RR (95% CI)	NNT (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: at least 50% pain intensity reduction							
Gabapentin	1800 to 3600	3	892	33	20	1.7 (1.3 to 2.2)	7.5 (5.2 to 14)
Pregabalin	300	3	535	30	11	2.7 (1.9 to 4.0)	5.3 (3.9 to 8.1)
	600	3	551	39	14	2.8 (2.0 to 3.9)	4.0 (3.1 to 5.5)
Outcome: at least 30% pain intensity reduction							
Pregabalin	300	1	191	41	17	2.4 (1.4 to 3.9)	4.2 (2.8 to 8.9)
	600	2	356	58	21	2.8 (2.0 to 3.8)	2.7 (2.2 to 3.7)
Outcome: Patient Global Impression of Change — excellent							
Gabapentin	1800 to 3600	2	563	15	6	2.7 (1.5 to 4.8)	11 (7.0 to 22)
Outcome: Patient Global Impression of Change — very good or excellent							
Gabapentin	1800 to 3600	4	1121	38	20	1.9 (1.5 to 2.3)	5.5 (4.3 to 7.7)

RR = risk ratio; NNT = number needed to treat to benefit; CI = confidence interval

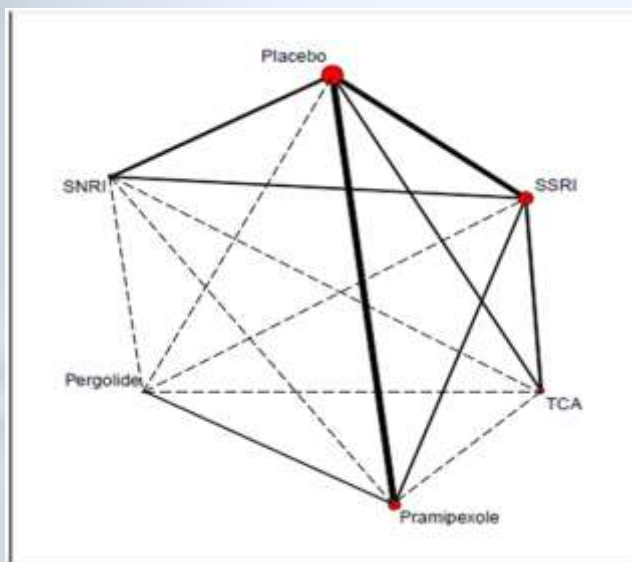
Reliable evidence in acute pain from the Cochrane Pain Group

NNT for at least 50% maximum pain relief over 4-6 hours



Network Meta-analysis

Network of RCTs where all trials have at least one intervention in common with another
Allows for indirect comparisons of interventions not studied head to head.
Relies on complex statistical analyses.



Comparative efficacy and acceptability of antidepressants in Parkinson's disease: a network meta-analysis.

Liu J, Dong J, Wang L, Su Y, Yan P, Sun S.
PLoS One. 2013 Oct 2;8(10):

Conclusions

- Evidence based medicine is a core skill for clinical pharmacists.
- Get to know the resources
- Learn to use the tools effectively
- Need to establish what is already known for your speciality

Three questions !

- A forest plot is a means to present an average ?
- Large values for numbers needed to treat (NNTs) show a bigger effect than small ones?
- Systematic reviews are the most reliable evidence?
- Answer YES(green) or NO(red)

Three questions !

- A forest plot is a means to present an average ? **YES**
- Large values for numbers needed to treat (NNTs) show a bigger effect than small ones? **NO**
- Systematic reviews are the most reliable evidence? **YES**

Your turn!

Critical appraisal exercise

- Selected parts of a review in handout
- Use the 10 questions to find out if the review is reliable
- Discuss in groups