Well Established Medical Use
Implications for clinical research

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What I will be talking about:

- WEU and it's assessment for EU monographs.
- What is a 'Good Study' ?
- RCT, ObS, and bias.
- EBM and WEU.
- What is a good design for a WEU study ?

Well Established Medical Use: 2001/83

Article 10a

By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature.

…and it's assessment

European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 7 September 2006
Doc. Ref. EMEA/HMPC/104613/2005

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

GUIDELINE ON THE ASSESSMENT OF CLINICAL SAFETY AND EFFICACY IN THE PREPARATION OF COMMUNITY HERBAL MONOGRAPHS FOR WELL-ESTABLISHED AND OF COMMUNITY HERBAL MONOGRAPHS / ENTRIES TO THE COMMUNITY LIST FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS / SUBSTANCES / PREPARATIONS

…and it's assessment

4. RECOMMENDATIONS FOR IMPLEMENTATION

4.1 Guidance on monographs for well-established herbal medicinal products

The concept relies on the thinking that the wide-spread medicinal use of a product within the Community for at least 10 years may have generated a sufficient body of conclusive scientific literature that will allow an assessment of safety and efficacy. In most cases, the product has been granted a marketing authorisation and data on pharmacovigilance and PSURs will be available. Experience resulting from pharmacovigilance will be crucial for the assessment of clinical safety. The legislation allows a broad spectrum of evidence that may be used in the assessment of efficacy. In addition to published controlled clinical trials, the assessment of safety and of efficacy may be based on non-controlled clinical studies, epidemiological studies such as cohort or observational studies etc.

…and it's assessment

In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy.In the absence of a controlled clinical trial a case-by-case assessment taking into account possible benefits, risks and types of disease may be acceptable, if clinical experience with the herbal medicinal product is well documented and supportive, conclusive (human) pharmacological data of good quality are available. Evidence of grade C/level IV supported only by pre-clinical data are not sufficient to make the clinical efficacy of a product recognised.

What is a ‘Good Study’ ?

A ‘study of good quality that substantiates efficacy’ is one that answers essential research questions about the efficacy of the product by using an appropriate design.

What are the essential questions about WEU-MPs?

- What we know about WEU-MPs:
  - ✓ The product is efficacious (it has been licensed for more than 10 years!)
  - ✓ The product is safe.

- What we often do not know (enough about):

  What are the modalities of WEU in real life?

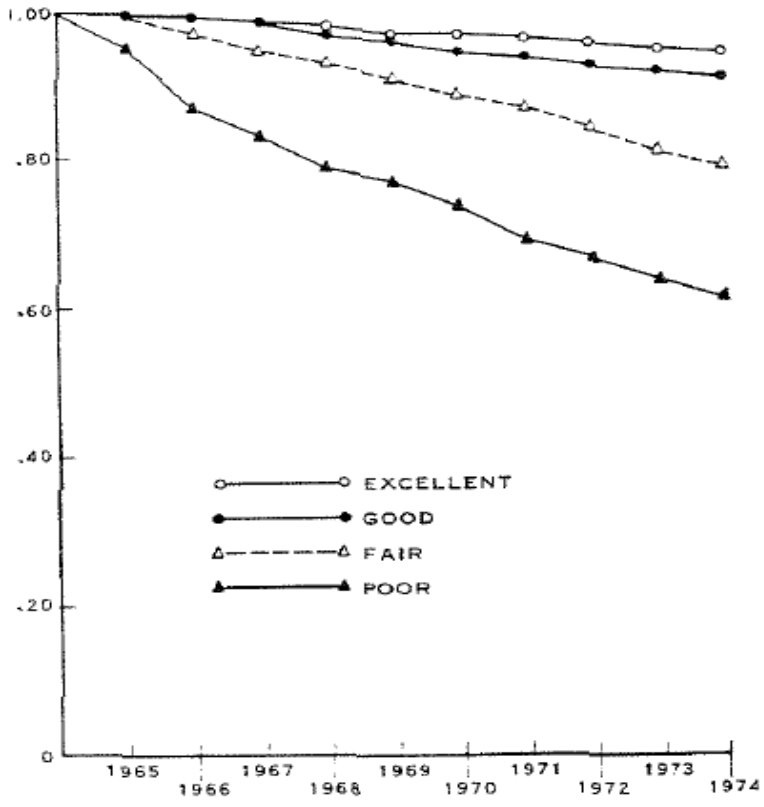
  How can the treatment benefit be optimised for the individual patient, especially in a non-RX setting?

What is typical of ‘non-RX practice’ ?

- The patient decides about the therapeutic goals.
- The patient decides about the modalities of the therapeutic strategy. (Hopefully well advised by a pharmacist or a doctor.)
- The patient decides how to apply the therapy and when to end it.

Is the patient, who acts out of his beliefs and his prejudices, competent enough? Is research on something diffuse like "non-RX practice" worthwhile?

Patient Well-Being and 10-Year Mortality



Perceived Heath and Mortality: A Nine-Year Follow-Up of the Human Population Laboratory Cohort.
Kaplan (1983).Am. J. Epidemiology 117: 292

From Nature.
For Health.

Dr. Willmar Schwabe Pharmaceuticals
www.schwabepharma.com

A good study has a good design !

What is an appropriate study design for the questions about WEU under real life conditions ?

Levels of evidence …

Level	Type of Evidence
I	Systematic Reviews of well controlled Randomized Controlled Trials (meta-analysis) or single RCT with narrow CI (confidence interval)
II	Systematic review cohort studies or lesser quality RCTs
III	Case controlled studies (non randomized)
IV	Case series (no control group)
(V)	Expert opinion (GOBSAT - Good Old Boys Sat Around Table)

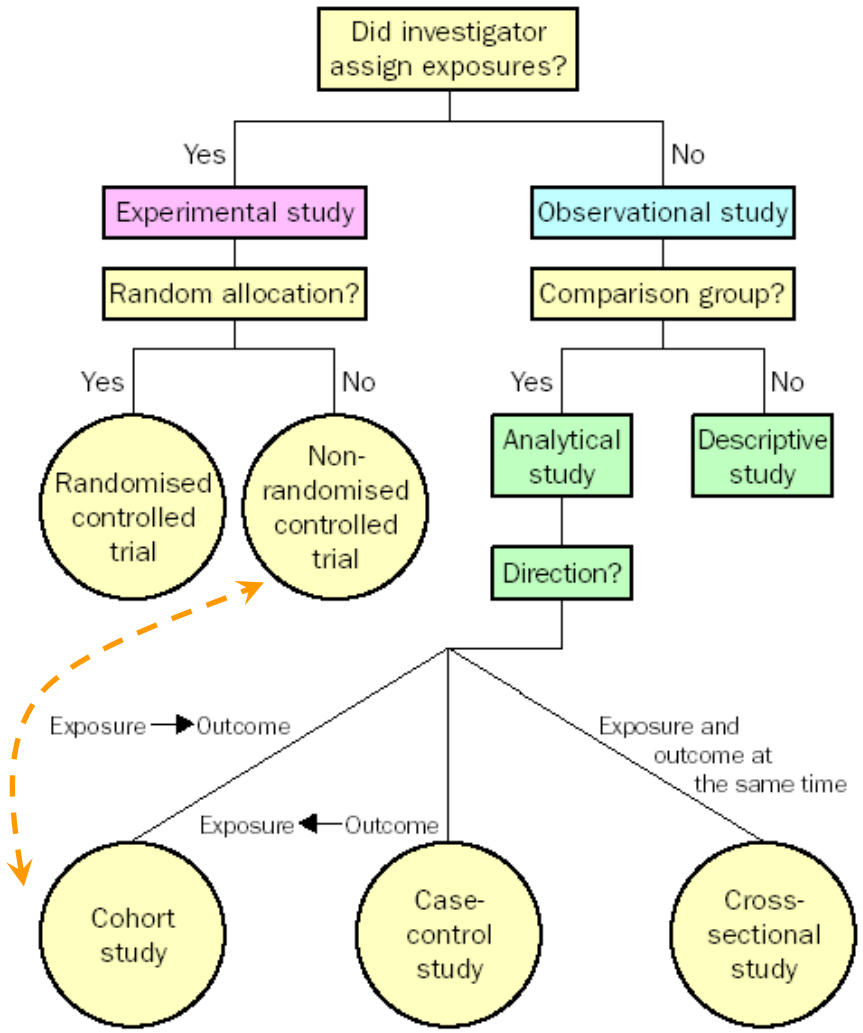


Figure 1: **Algorithm for classification of types of clinical research**

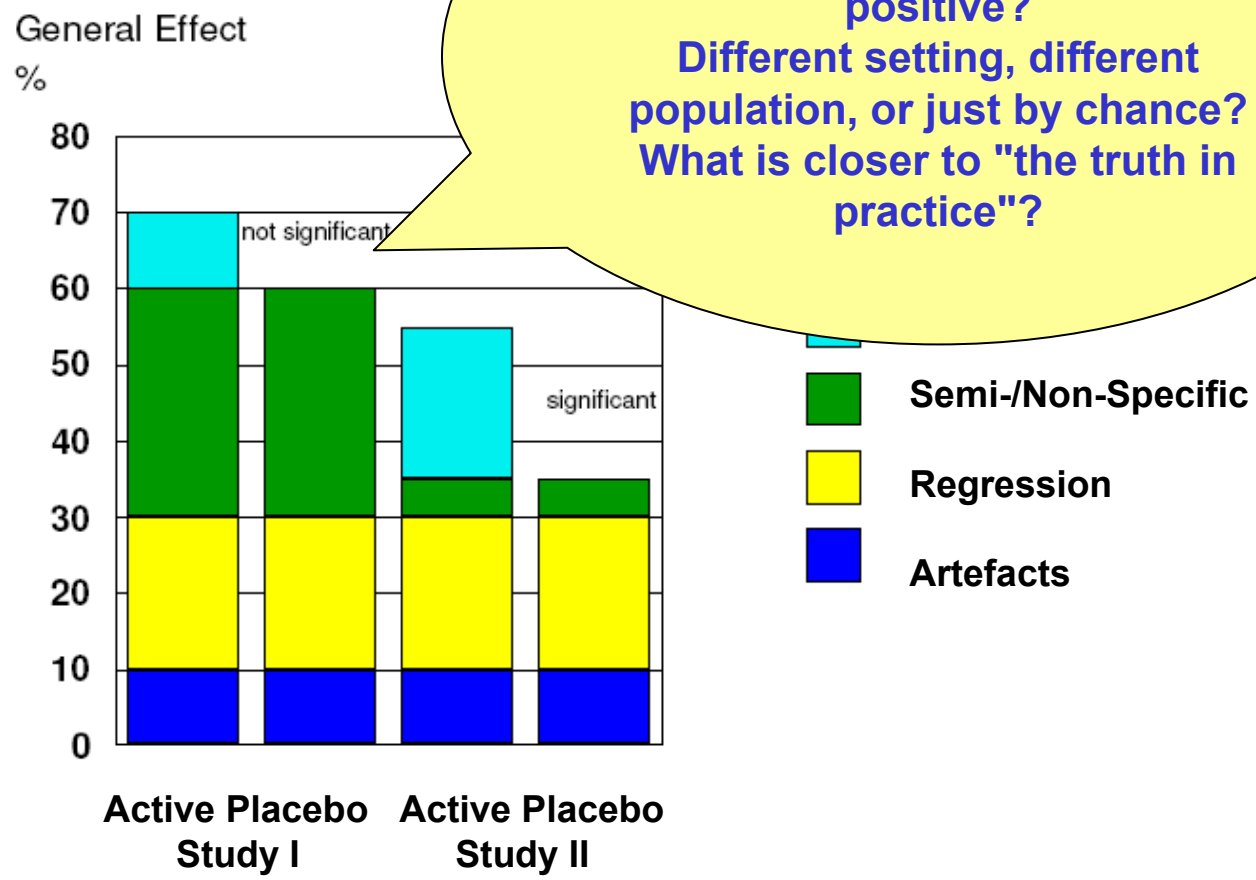
David A Grimes, Kenneth F Schulz

THE LANCET • Vol 359 • January 5, 2002 • www.thelancet.com

Experimental studies will always be, observational studies can be, clinical trials if they are not "non-interventional" (Dir 2001/20).

Observational studies will usually be, but do not necessarily have to be, pragmatic trials.

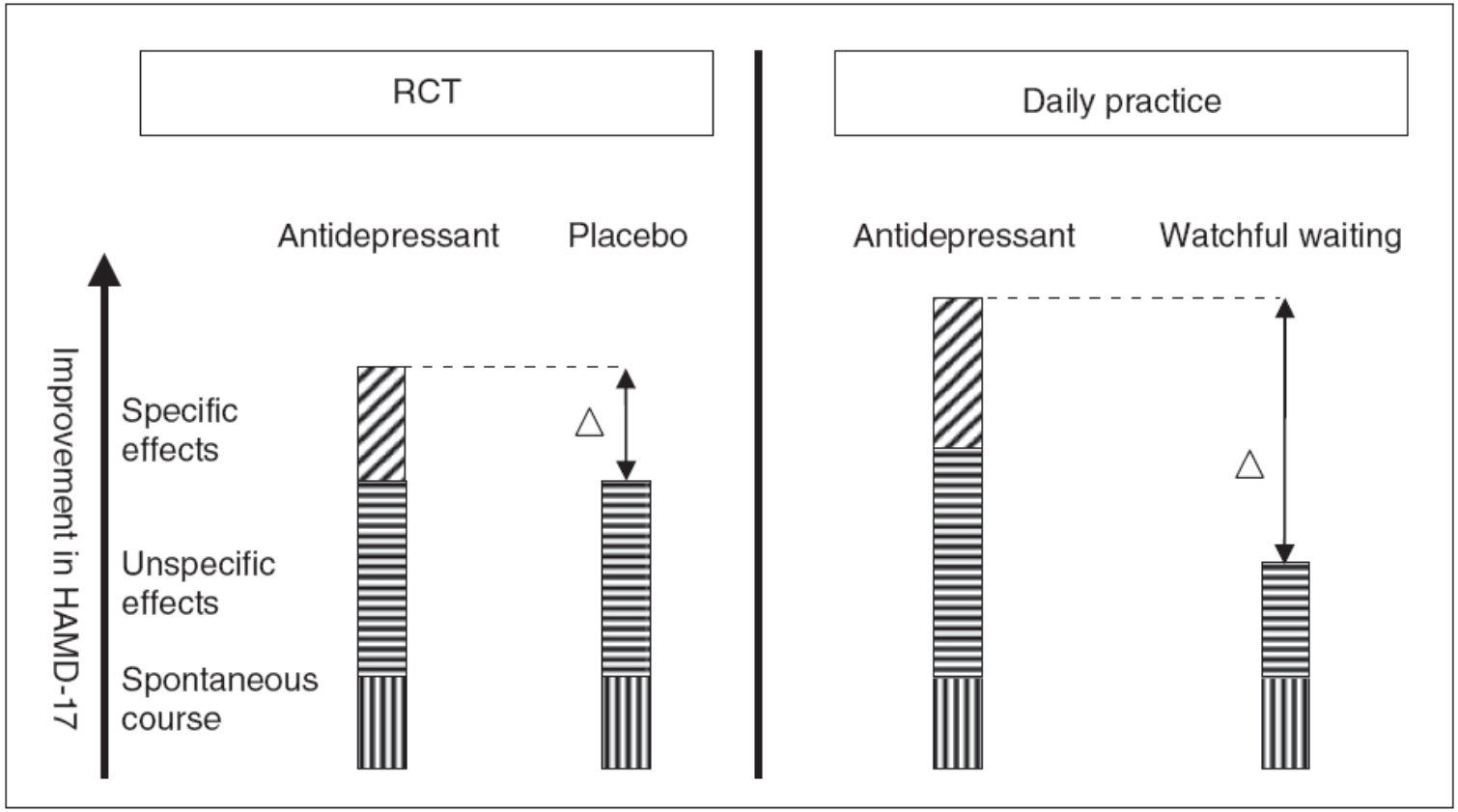
The treatment parado



Is this effect still relevant?
Is the benefit-risk ratio still positive?
Different setting, different population, or just by chance?
What is closer to "the truth in practice"?

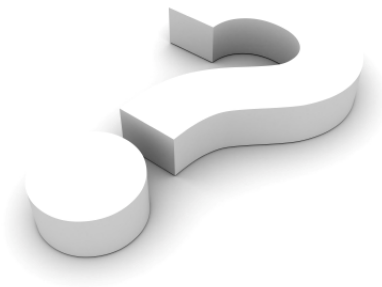
Circular instead of hierarchical: methodological principles for the evaluation of complex interventions. Walach (2006) BMC Med Res Methodol. 6:29.

… and in practice (Major Depression)



The clinical significance of antidepressant treatment effects cannot be derived from placebo-verum differences.
Hegerl U (2010): J Psychopharmacology 24, 445-448

So, let's try with an RCT !



The RCT: Gold standard or golden calf? *

- Observational studies do not use randomisation and blinding of the patient.
- These are important tools to control for bias (selection, information, confounding) and to enable valid statistical comparisons.
- RCTs can best prove specific efficacy.

  (isn't that a circular conclusion?)
- The RCT message to the patient is:
  - We do not know which treatment is really working.
  - You are member of a treatment group, not relevant as an individual person.

** The double-blind, randomized, placebo-controlled trial: Gold standard or golden calf? Kaptchuk TJ (2001). J Clin Epidemiology 54: 541-549*

The RCT: Gold standard or golden calf?

- Randomisation and blinding do not happen in medical practice.
- A ‘specific effect’ as measured by an RCT (difference between active treatment and placebo) is of limited importance for practical use. In many instances, it is the perceived total effect that counts.
- Informed consent, the knowledge of being randomised and masking all influence the benefit perceived by the patient.

How relevant are RCT results for WEU?

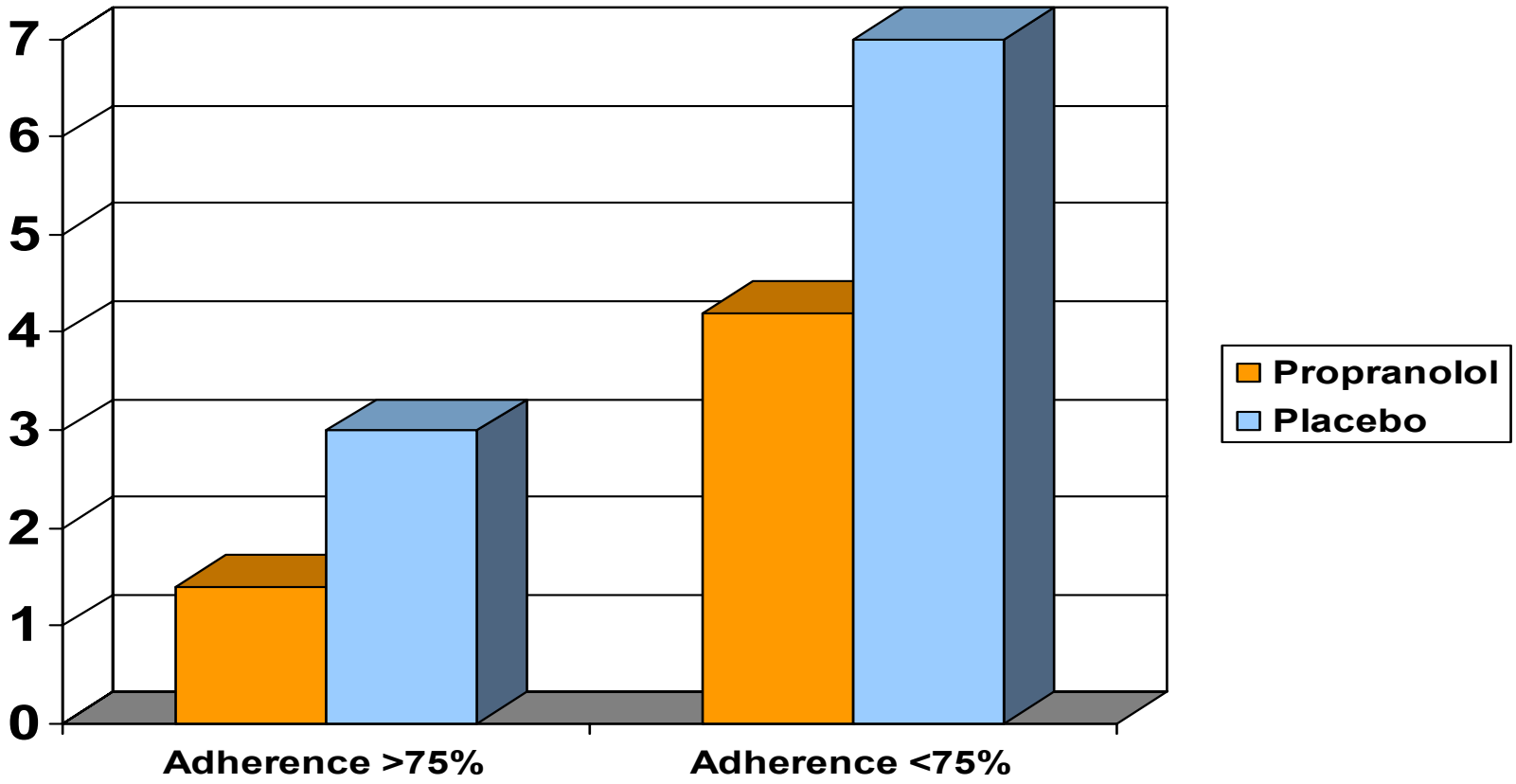
In WEU the objective is to enable best patient benefit.

So, what matters is how a drug can be applied in such a way that the patient chooses to adhere to the therapy because

- he expects it to be effective and
- believes it is the best possible treatment for HIM
- on the background of his knowledge about and his pre-experience with the product.

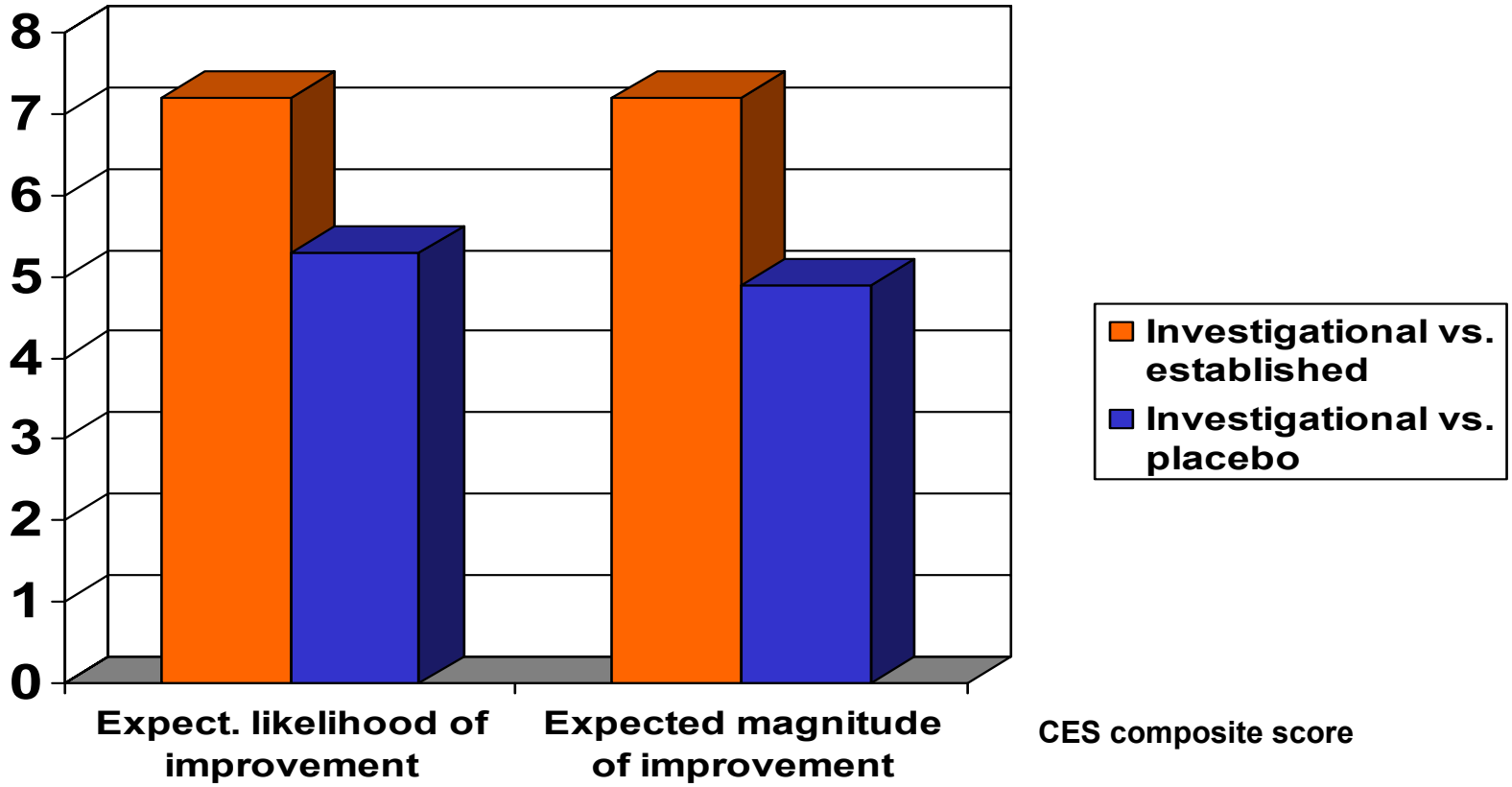
WEU research is about the drug and the best possible setting to use it.

Adherence counts: Treatment adherence and mortality 1y after MI (%)



Adherence to treatment and health outcomes.
Horwitz RI, Horwitz SM.
Arch Intern Med (1993) 153: 1863-1868

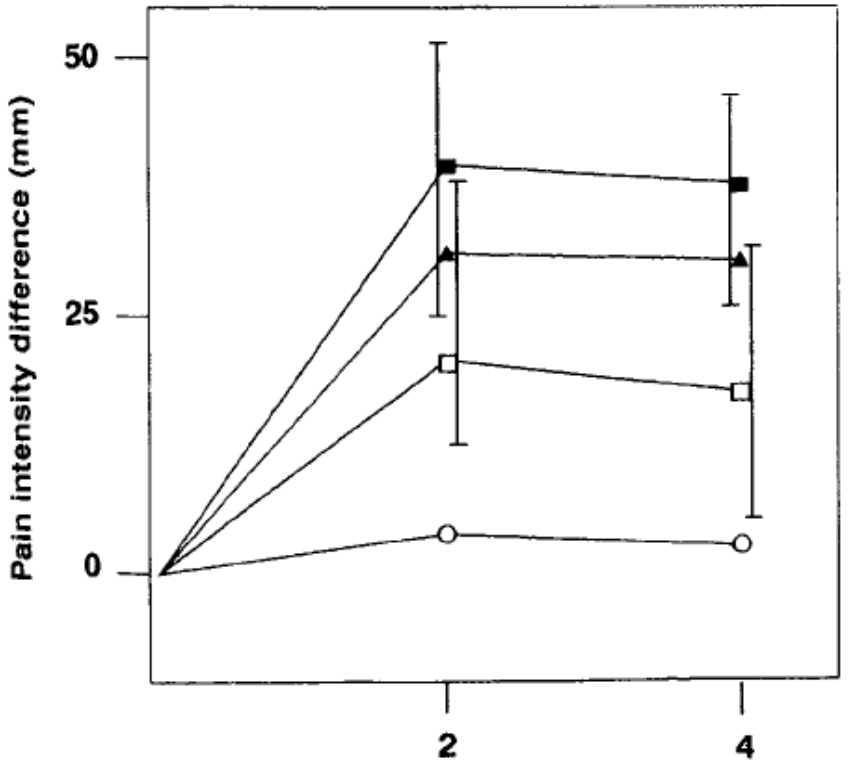
Expectation: Influence of study design



Study design affects participant expectations: a survey.
Rutherford BR et al.
J Clin Psychopharmacol, 2009.

Expectation: Influence on outcome

Should we tell trial patients that they might receive placebo? Skovlund E. Lancet (1991) 337: 1041



Median pain intensity difference 2 and 4 h after medication.

■ = paracetamol, trial 2 (including pilot study patients).
▬ = paracetamol, trial 1.
▲ = naproxen, trial 2.
- = placebo, trial 1.

Non-parametric 95% confidence intervals given for two paracetamol groups being compared.

Belief in individual best treatment

TABLE I—*The commonest presenting symptom in the group of 200 patients*

Symptom	No	Symptom	No
Cough	31	Tiredness	8
Sore throat	29	Chest pain	6
Cold	16	Nasal congestion	5
Abdominal pain	16	Muscular pains	5
Back pain	10	Earache	4
Giddiness	9	Painful arm	4
Leg pain	8	Breast pain	4
Headache	8	Neck pain	4

General Practice Consultations: is there any point in being positive?
Thomas KB. (1987): BMJ 294: 1200-1202

Belief in individual best treatment

In the positive consultations the patient was given a firm diagnosis and told confidently that he would be better in a few days. If no prescription was to be given he was told that in the doctor's opinion he required none, and if a prescription was to be given that the treatment would certainly make him better. The negative consultation was an artificial consultation, devised so that no firm assurance was given. This was done by the doctor making one statement: 'I cannot be certain what is the matter with you." If no prescription was to be given the following words were added: "And therefore I will give you no treatment." If a prescription was to be given the patient was told: "I am not sure that the treatment I am going to give you will have an effect." The negative consultations were brought to a close by telling the patient that if he or she was no better in a few days to return to the doctor.

"Treatment" was a prescription for tabs thiamine hydrochloride 3 mg, used as a placebo, and "no treatment" was no prescription.

General Practice Consultations: is there any point in being positive?
Thomas KB. (1987): BMJ 294: 1200-1202

Belief in individual best treatment

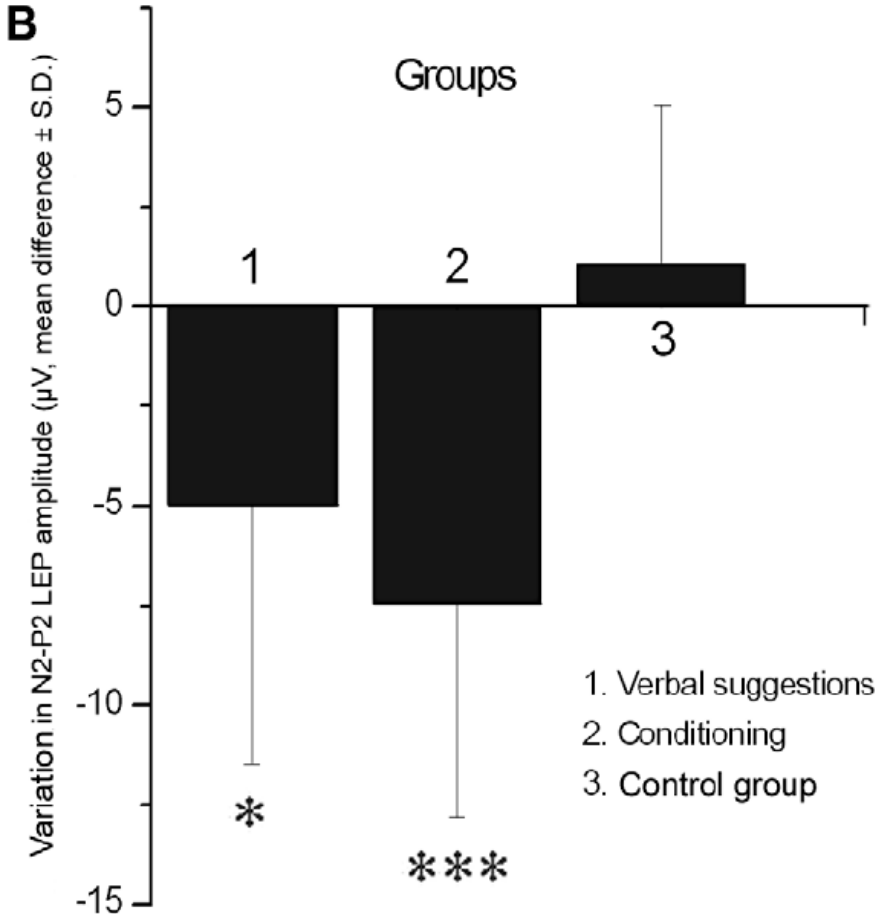
TABLE III—*Numbers (and percentages) of patients who got better*

	Positive consultations		Negative consultations	
	Treated (n=50)	Not treated (n=50)	Treated (n=50)	Not treated (n=50)
Men	14	10	5	9
Women	18	22	16	9
Total	32	32	21	18
Grand total	64		39	

$p<0{\cdot}001$.

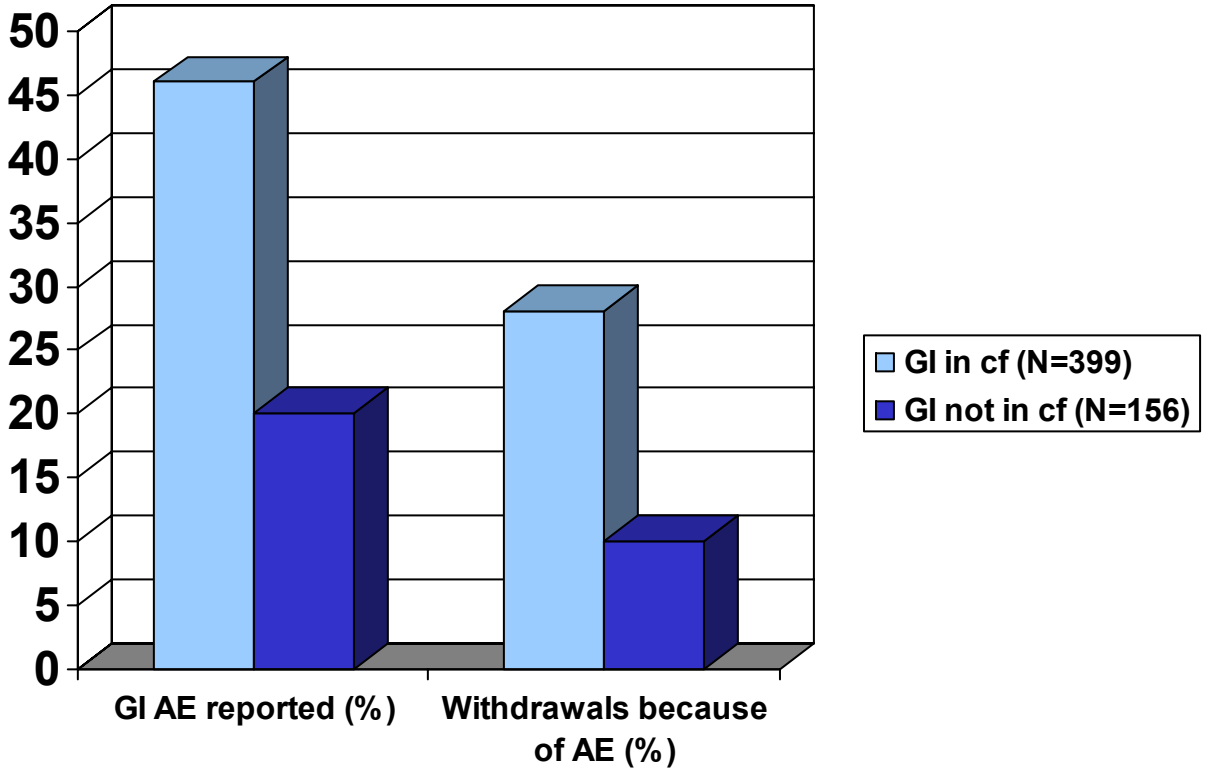
General Practice Consultations: is there any point in being positive?
Thomas KB. (1987): BMJ 294: 1200-1202

Positive pre-experience improves improvement



Learning potentiates neurophysiological and behavioral placebo analgesic responses. Colloca L (2009). Pain 139, 306-314

Consent and tolerability



The consent form as a possible cause of side effects.
Myers MG et al.
Clin Pharmacol Ther (1987) 42: 250-253

It is not easy to transfer RCT results to the WEU situation!

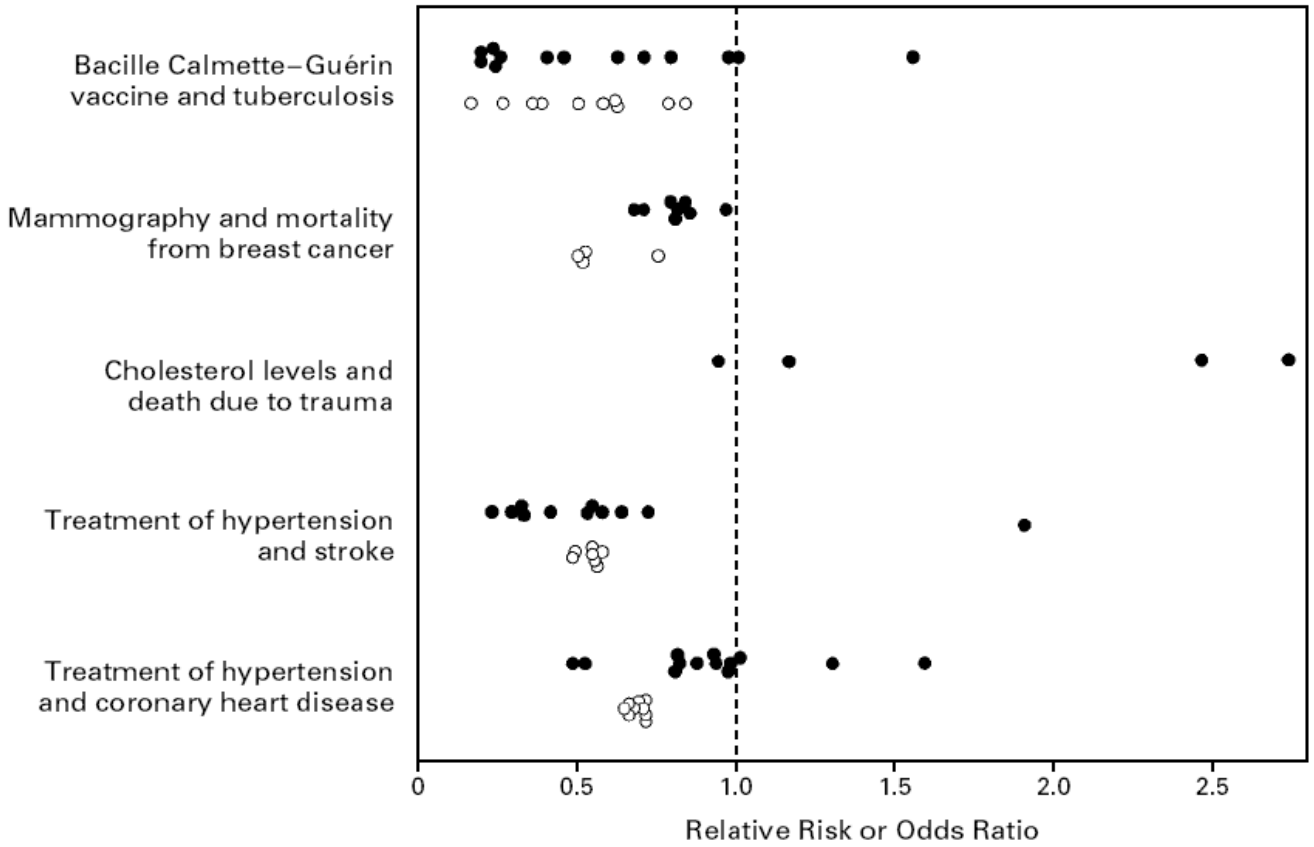
Real life is different !

Real-life WEU is quite different from the RCT setting:

- The patient is aware of the therapy and it's possible benefits and risks:
  - ↷ No masking (but blinding of the study observer is possible)
- The patient receives his preferred therapy:
  - ↷ No randomisation

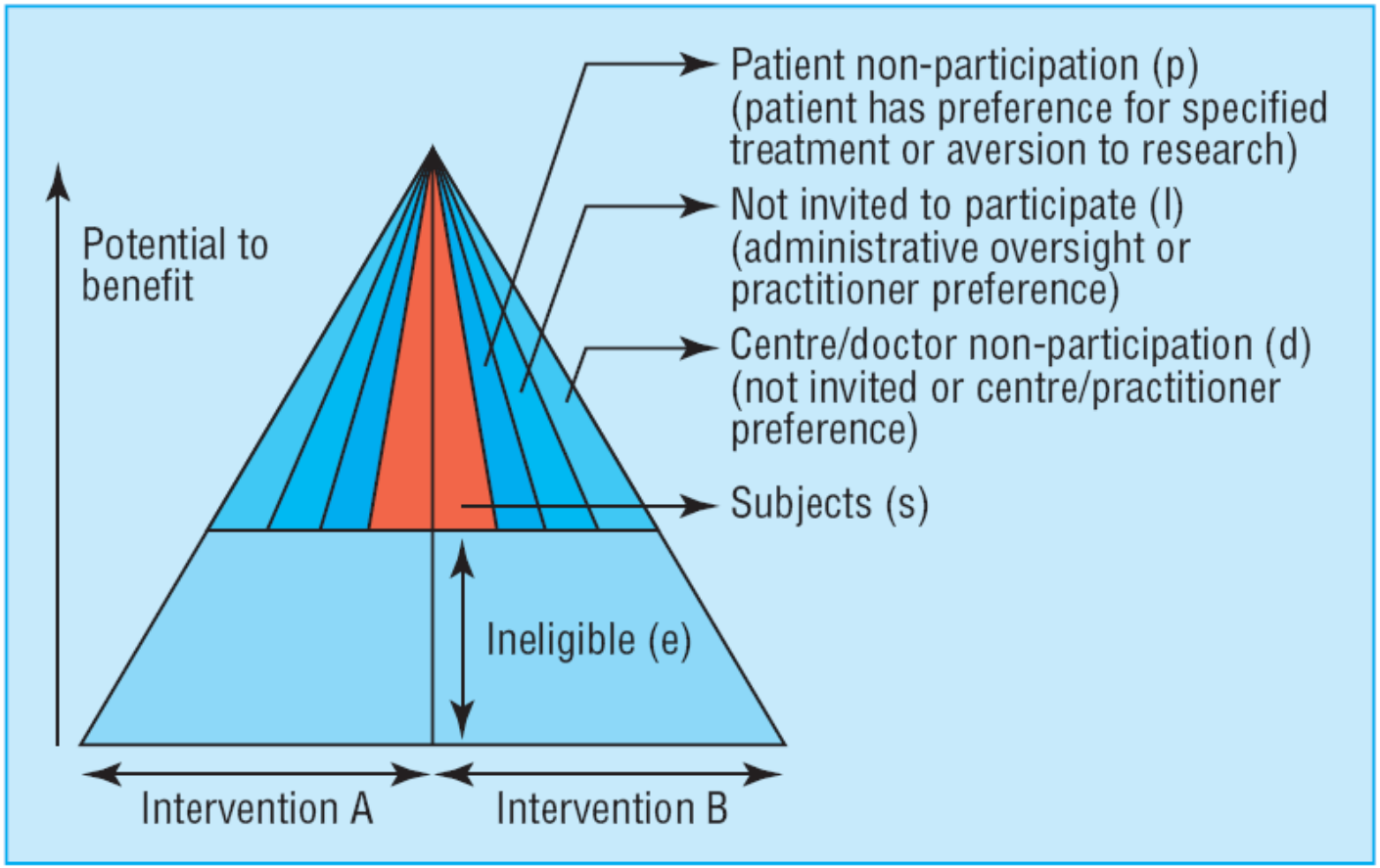
>> Are non-interventional (=observational) studies a 'good' alternative?

Observational trials are not that bad



Randomized, controlled trials, observational studies, and the hierarchy of research designs.
Concato J, Shah N, Horwitz RI.
N Engl J Med. 2000 Jun 22;342(25):1887-92.

… and do not that much show non-consent bias



Interpreting the evidence: choosing between randomised and non-randomised studies
McKee M et al. BMJ 1999;319:312–5

Observational trials : criteria

Panel 1: **What to look for in observational studies**

Is selection bias present?
In a cohort study, are participants in the exposed and unexposed groups similar in all important respects except for the exposure?

In a case-control study, are cases and controls similar in all important respects except for the disease in question?

Is information bias present?
In a cohort study, is information about outcome obtained in the same way for those exposed and unexposed?

In a case-control study, is information about exposure gathered in the same way for cases and controls?

Is confounding present?
Could the results be accounted for by the presence of a factor—eg, age, smoking, sexual behaviour, diet—associated with both the exposure and the outcome but not directly involved in the causal pathway?

If the results cannot be explained by these three biases, could they be the result of chance?
What are the relative risk or odds ratio and 95% CI?[11,12]

Is the difference statistically significant, and, if not, did the study have adequate power to find a clinically important difference?[13,14]

If the results still cannot be explained away, then (and only then) might the findings be real and worthy of note.

Bias and causal associations in observational research. Grimes DA, Schulz KF. Lancet (2002) 359: 248–52

Observational trials : criteria

Panel 2: **Criteria for judgment of causal associations**[17,42,43]

Temporal sequence
Did exposure precede outcome?

Strength of association
How strong is the effect, measured as relative risk or odds ratio?

Consistency of association
Has effect been seen by others?

Biological gradient (dose-response relation)
Does increased exposure result in more of the outcome?

Specificity of association
Does exposure lead only to outcome?

Biological plausibility
Does the association make sense?

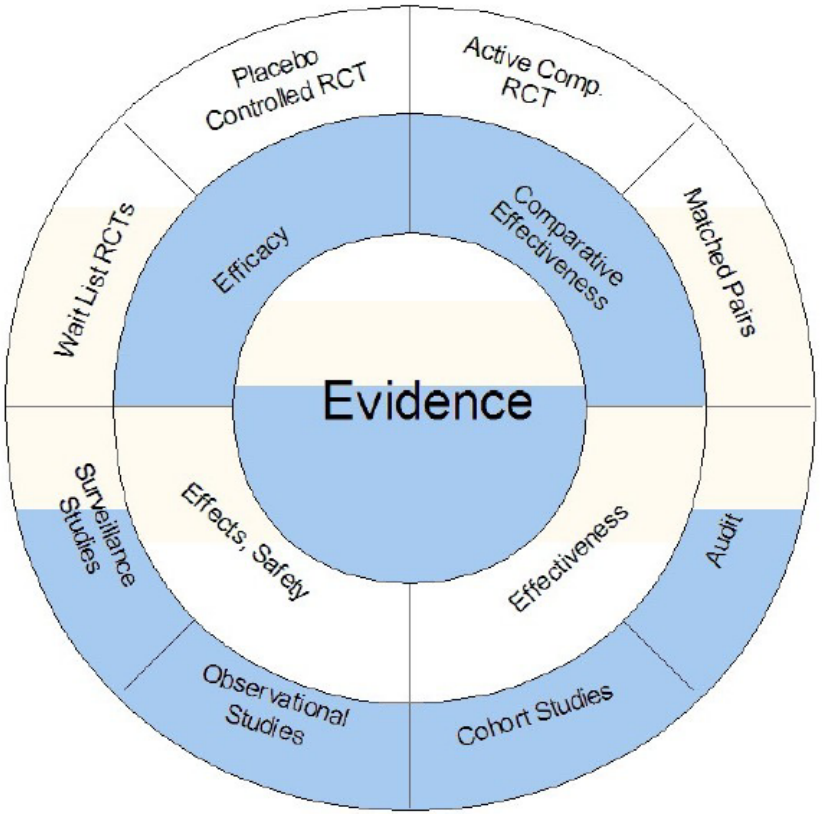
Coherence with existing knowledge
Is the association consistent with available evidence?

Experimental evidence
Has a randomised controlled trial been done?

Analogy
Is the association similar to others?

Bias and causal associations in observational research. Grimes DA, Schulz KF. Lancet (2002) 359: 248–52

Levels of evidence - 2



Circular instead of hierarchical: methodological principles for the evaluation of complex interventions. Walach (2006) BMC Med Res Methodol. 6:29.

Is that in line with "Evidence Based Medicine" ?

"The practice of evidence based medicine means integrating individual clinical expertise with the best available external medical evidence from systematic research …

EbM is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions …"

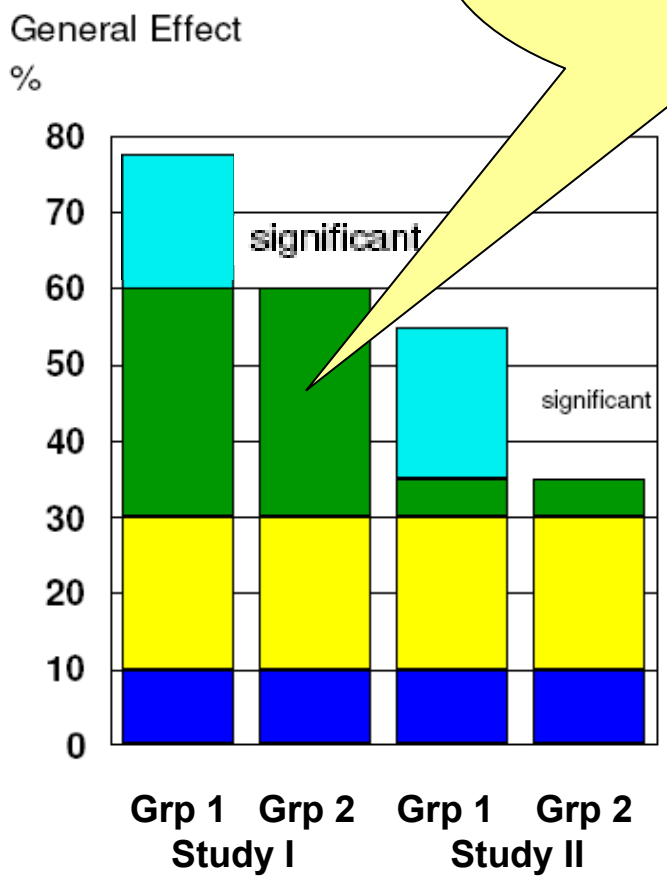
Sackett DL: Evidence-based medicine: What it is and what it isn't. Brit. med. J. 312 [1996] 71-72

Herbal ? I love it !

From Nature.
For Health.

Dr. Willmar Schwabe Pharmaceuticals
www.schwabepharma.com

Semi-specific herbal group effects are specific effects of herbals.



- Specific, whatever that means
- Semi-/Non-Specific
- Regression
- Artefacts

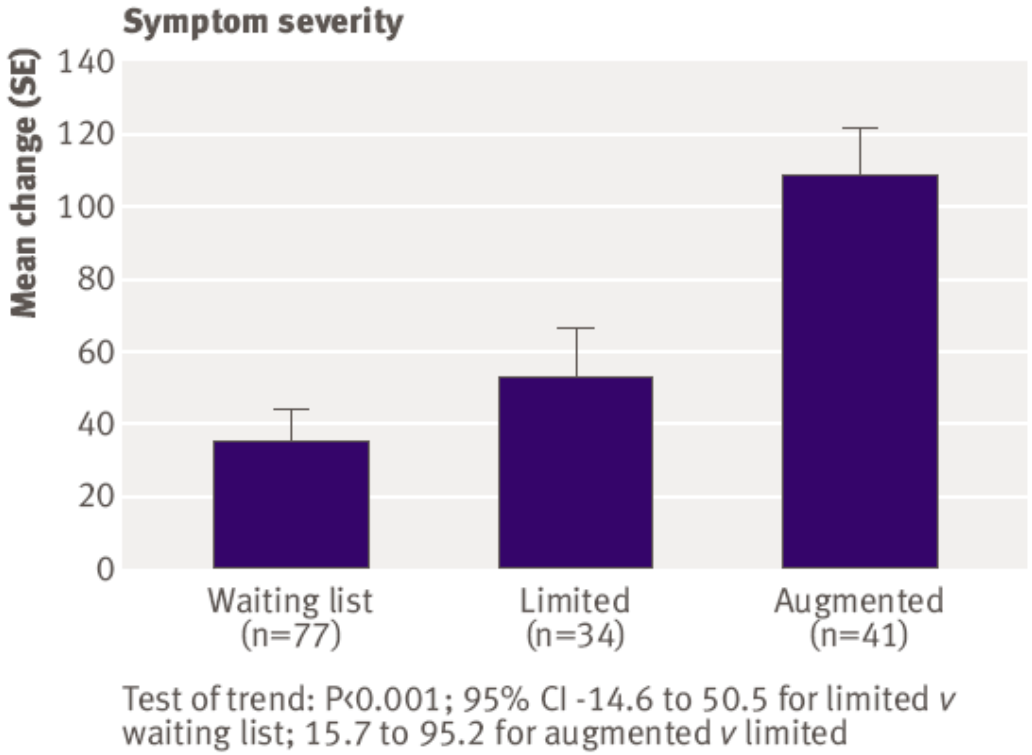
A good quality Well-Established Use study …

… is a study well designed
to tell us:

How the product is best used
(in order to achieve
a maximum total effect
for the patient).
Choose your design with empathy!

Thanks !

The magnitude of the placebo effect is context-dependent !



Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome.
Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, et al.
BMJ. 2008 May 3;336(7651):999-1003.

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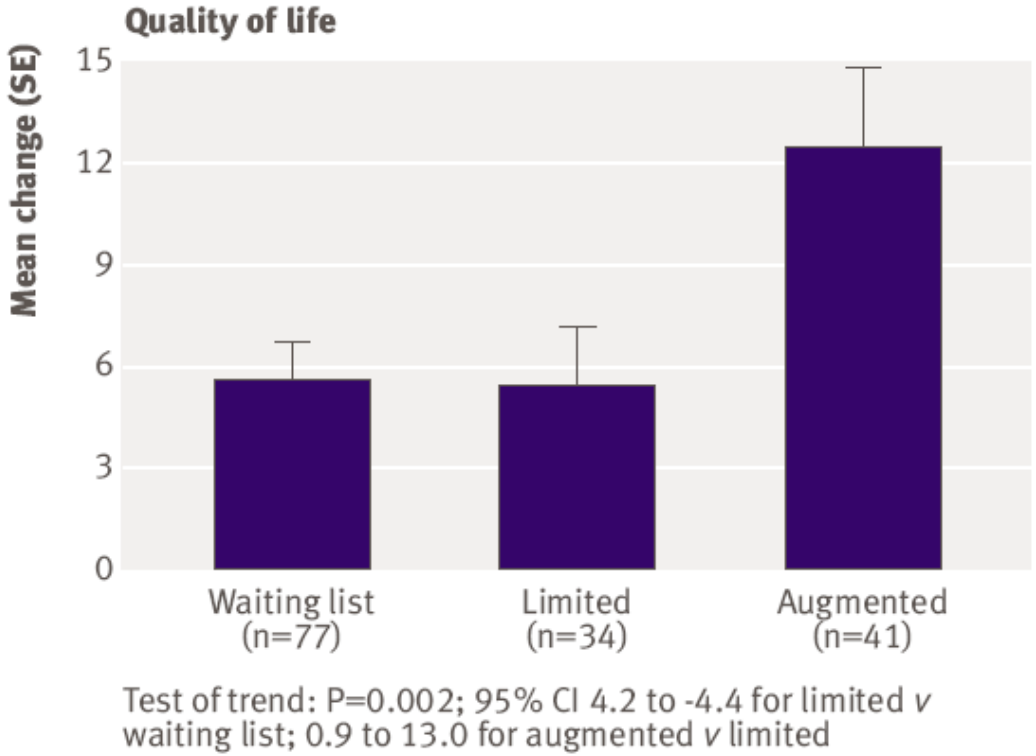

Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome.
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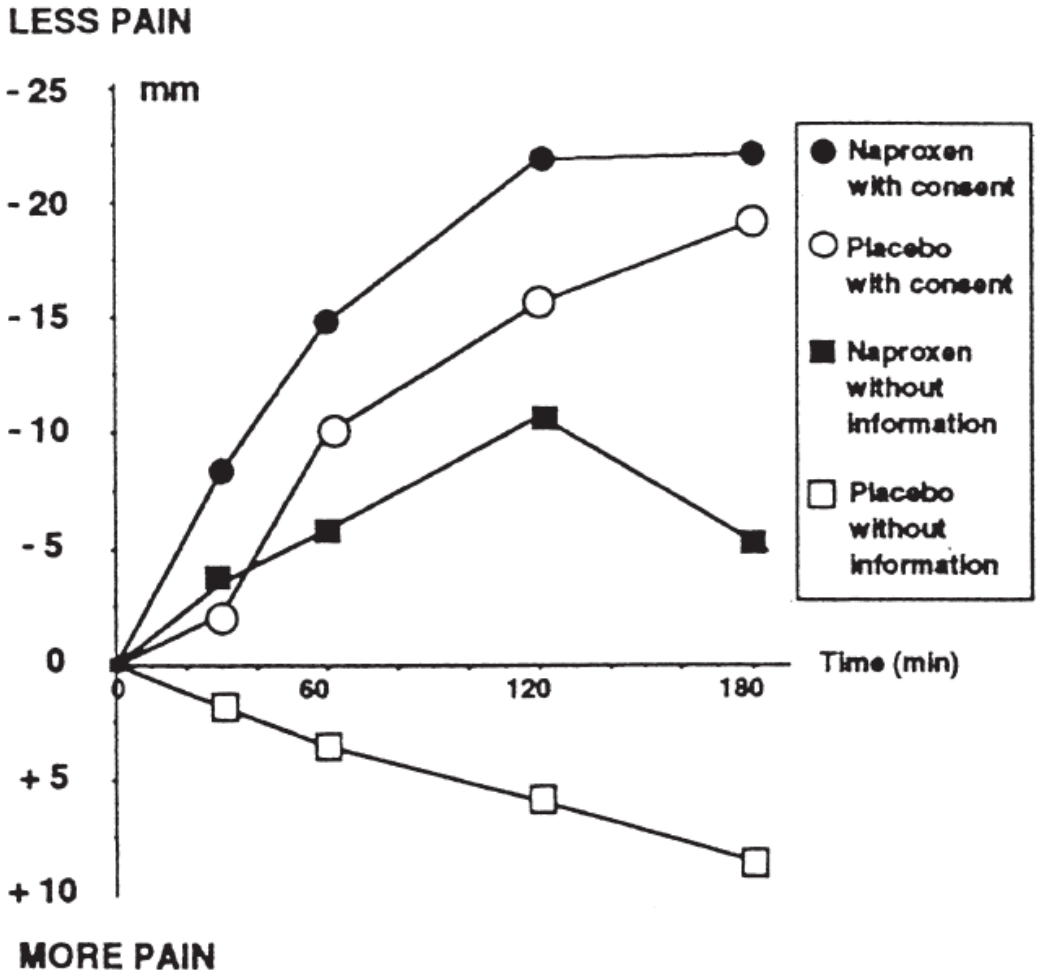
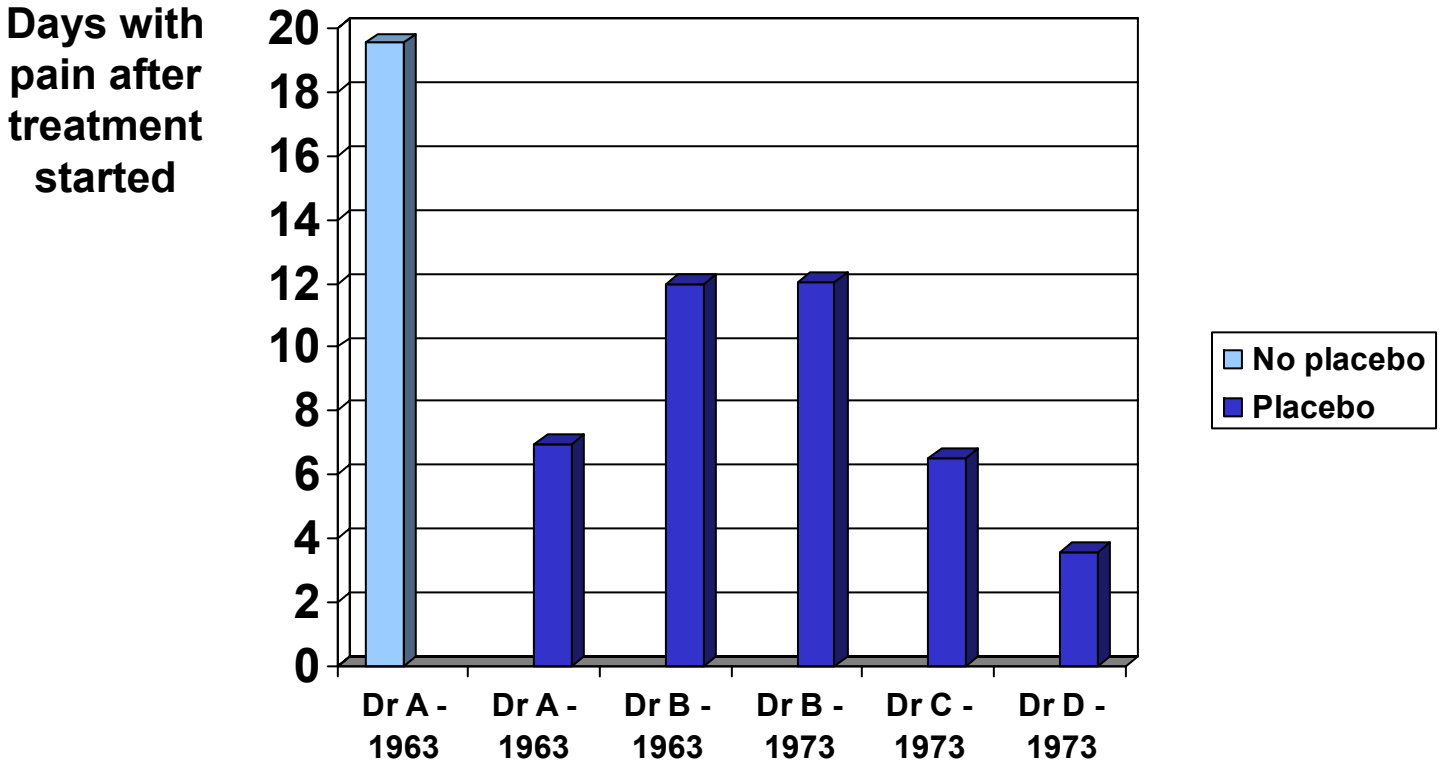
BMJ. 2008 May 3;336(7651):999-1003.

Consent bias: Consent increases effects but lowers treatment difference



Randomized clinical trial of the effect of informed consent on the analgesic activity of placebo and naproxen in cancer pain. Bergmann JF. Clin Trials Meta-Anal 1994;29:41–7.

Investigator Bias: Duodenal ulcer



A study of the variations in the response regarding duodenal ulcer when treated with placebo by different investigators.
Sarles H (1977): Digestion 16: 289-292.