Evidence Based Practice Primer

Outline

- Evidence Based Practice (EBP)
- EBP overview and process
- Formulating clinical questions (PICO)
- Searching for EB answers
- Trial design
- Critical appraisal
    - Assessing the validity of trial design
- Interpreting results
    - p values and confidence intervals
    - Statistical vs clinical significance
    - Magnitude of effect (ARR, RRR, NNT)

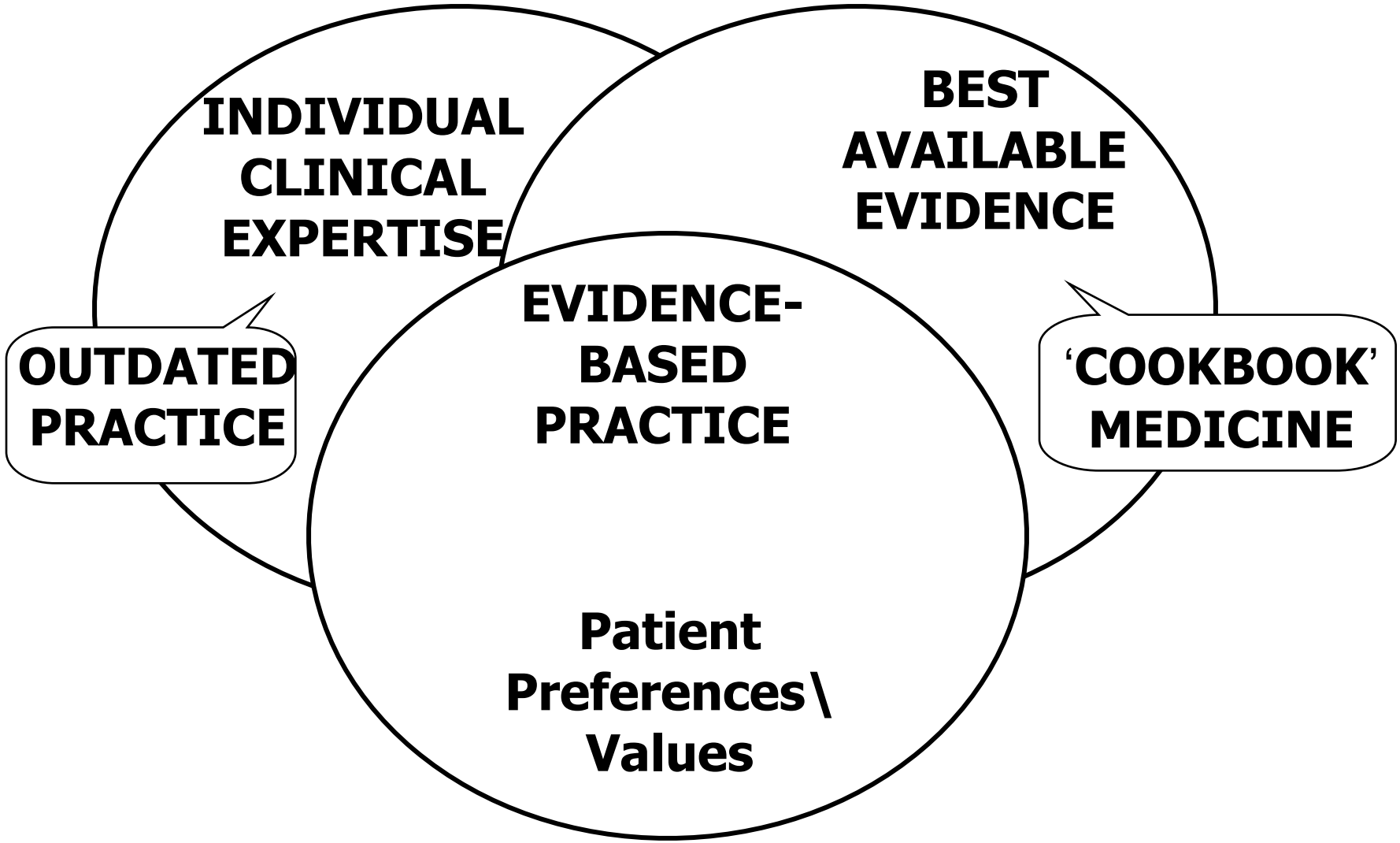
What is Evidence-Based Practice?

"The integration of best research evidence with clinical expertise and patient values"

Sackett et al 2000

When these three elements are integrated, clinicians and patients form a diagnostic and therapeutic alliance with optimized clinical outcomes and quality of life

EVIDENCE-BASED PRACTICE



What EBP is Not:

EBP is not cook-book medicine

Evidence needs translation to patient's unique features and values

EBP is not cost-cutting practice

May actually result in increased costs for some patients and/or conditions

Why Sharpen your Critical Appraisal Skills?

Even highly reputable journals publish poor and/or misleading information

Improved decision making about the management of patients

Tool to efficiently stay current with advancing health care knowledge while filtering out studies not worth your time

A method of managing and utilizing the enormous amount of medical literature

Help solve clinical problems

Can even be fun & make your practice more interesting

Knowledge's Half Life:

"My students are dismayed when I say to them, 'Half of what you are taught as medical students will in 10 years have been shown to be wrong. And the trouble is, none of your teachers knows which half.'"

Dr. Burwell, Dean of Medicine, Harvard University

The Process

Clinical Scenario

Clinical Question (PICO)

Search

Critical Appraisal

Integrate & Apply

Barriers to EBP

- Limited awareness/knowledge
- Limited time
- Limited amount of well designed trials in your practice area
- Lack of motivation
    - Lack of skills or resources
    - Lack of financial incentives
- Inadequate literature searching skills
- Abundance of information

Clinical Questions (PICO)

Patient
- Description of the most important characteristics of the patient or target disorder

Intervention
- What do you want to do for the patient?
- Could include exposure, diagnostic test, prognostic factor, surgery, therapy or patient's perception

Comparator (s)
- Relevant alternative(s) most often considered for this type of patient

Outcome
- Clinical outcome of interest to you and your patient

Why all the fuss about a good clinical question?

With limits on time, it is important to ask questions that by design focus on evidence that is directly relevant to the patient's clinical needs and our knowledge needs

They can suggest high yield search strategies

Questions suggest forms that useful answers might take

PICO: Case 1

A 25 yo male comes into your office with symptoms of Major Depressive Disorder (that meet the criteria in the DSM IV TR. This is his second episode (in 2 yrs) and he has tried citalopram (with little benefit after 6 wks).

Patient

Intervention

Comparison

Outcome

PICO: Case 2

A 56 yo female with 5 year history of Type 2 DM has come to your office. Her family physician gave her metformin 500 mg bid and she says her HbA1C is 8.5% and she wants some natural therapies. What should she do?

Patient

Intervention

Comparison

Outcome

The Question Defines the "Best Evidence"

- Therapeutic intervention
  - RCT or systematic review/meta-analysis
- Rare side effect
  - Case control study
- Exposure to a potential toxin
  - Cohort study
- Evaluation of a new drug by Medicare
  - Pharmacoeconomic analysis

Trial Designs for Therapy Questions

Randomized controlled trial (RCT)

Systematic review (SR)

- A systematic (and hopefully rigorous) process to identify, synthesis and evaluate the available literature

Studies are:

- Identified according to an explicit search strategy
- Selected by defined inclusion & exclusion criteria
- Evaluated against consistent methodological standards

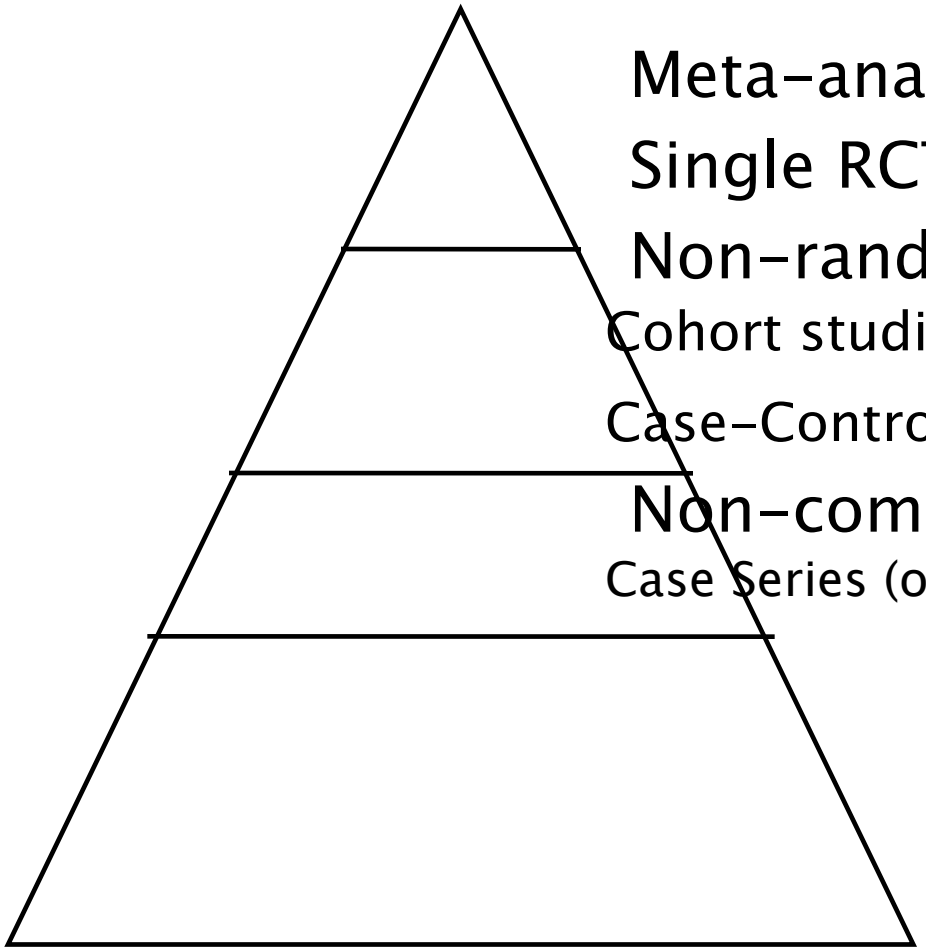
Meta-analysis (MA)

- A statistical process for quantitatively estimating the net benefit/risk from the results of the included studies

Where do you begin?

- Textbooks
- Journals
- Phone a friend
- Medline
- The Cochrane Library
- Evidenced based journals
  - ACP Journal Club, EBM
- Internet websites
  - Drug information websites
  - Evidence-based practice websites
  - Therapeutic specialty websites
  - Healthcare websites

The Hierarchy of Evidence for Therapy Studies



Meta-analysis of RCTs

Single RCTs

Non-randomized comparative studies

Cohort studies

Case-Control studies

Non-comparative studies

Case Series (open trial)

Case reports

Expert opinion

Synopses

Evidence-based journal abstracts and commentaries

Summary of reviews or individual studies

Easy to interpret & digest

Highly efficient

Detailed information readily available

Where Would I Find a Synopses?

Infopoems

Clinical Evidence on line

Bandolier

Evidence-Based Medicine

Therapeutics Initiative

ACP journal club

http://therapeuticseducation.org/useful-links

Efficiently Appraising 'Usable Evidence'

Right patient population (external validity)

Study design (right for the question?)

Internal validity

Results

are they meaningful and useful?

outcome measure?

can they be applied to my CQ?

Top 5 trial design features of prospective controlled trials

1. Randomized
2. Double blind
3. Allocation concealment
4. > 80 % of patients at study completion
5. Important, valid clinical outcomes selected

Why randomize?

Assessing the effectiveness of a treatment requires a comparison

In non-randomized comparisons, other factors may explain any differences observed (confounding)

Randomization controls for both known and unknown confounders

(Confounders ≈ risk factors)

Allocation Concealment

Shields those who admit patients into a trial from knowing future assignments

Happens before and during randomization process

"The decision to accept or reject a patient must be made, and informed consent obtained, without knowledge of the treatment to be assigned"

Schulz, 1995

Blinding

Unlike allocation concealment, this may not always be possible

Happens after randomization

Three main groups to consider:

- Patient
- Treatment team
- Treatment evaluator

p-value

The probability of the data, or more extreme data, occurring in the long run when there is NO treatment effect; i.e. how often this result or one more extreme will occur by chance alone

p-value

The p-value tells us if the difference was due to chance

p=0.013…what does that mean?

1.3% chance the difference was due to just chance (T or F)

98.7 % chance the difference was due to the intervention (T or F)

What can account for the difference?

1. A true difference
2. Bias
3. Confounding factors
4. Random error (chance)
5. All of the above

p-value

The p-value does NOT tell us …

If the difference is valid

If the difference is clinically meaningful

If the difference is real

If the drug works

Etc.

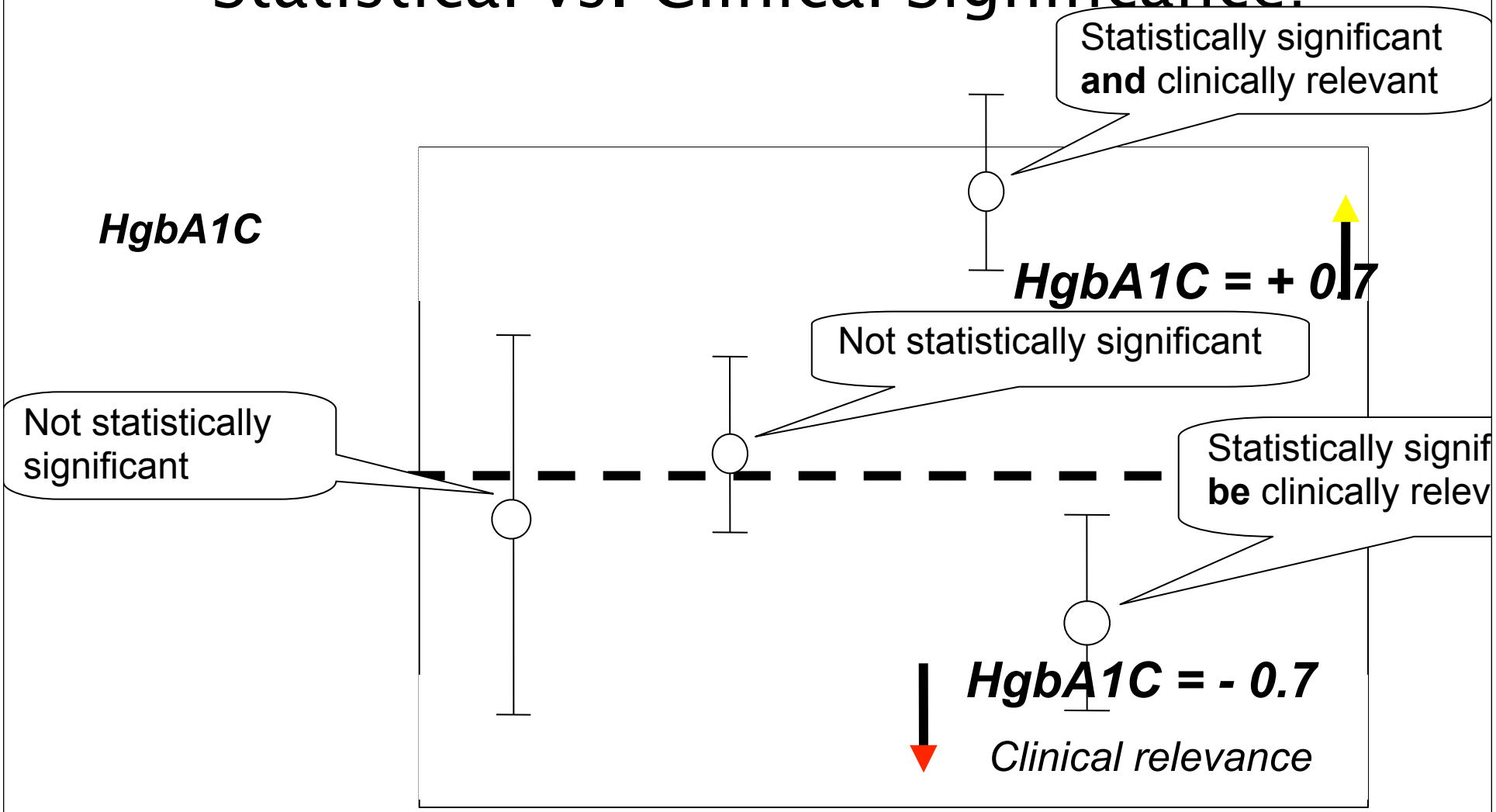
What is a Confidence Interval?

- Quantifies the uncertainty in measurement
  - A measure of the precession of the “effect estimate” from the study
- Usually reported as 95% CI
  - In a very large number of repetitions of the study, 95% of all CIs obtained will contain the “true” value of the treatment effect in the population studied (assuming random sampling)

Primary Prevention Statins & Mortality

Study	Risk Estimate	Authors Conclusion
BMJ 2009;338:b2376	0.88 (0.81-0.96)	Decreases mortality
Arch Intern Med 2010;170:1024-1031	0.91 (0.83-1.01)	∅
Arch Intern Med 2005;165:725-730	0.86 (0.76 -0.99)	Decreases mortality
Arch Intern Med 2006;166:2307-2313	0.92 (0.84-1.01)	∅
J Am Coll Cardiol 2008;52:1769-81	0.93 (0.87-0.99)	Decreases mortality

Statistical vs. Clinical Significance:



Typical Radio, TV, and Newspaper Reports

"Aspirin produces a 30% reduction in heart attacks"

"Treating high blood pressure reduces the chance of strokes by 40%"

"Cholesterol lowering drug decreases chance of heart attacks by 35%"

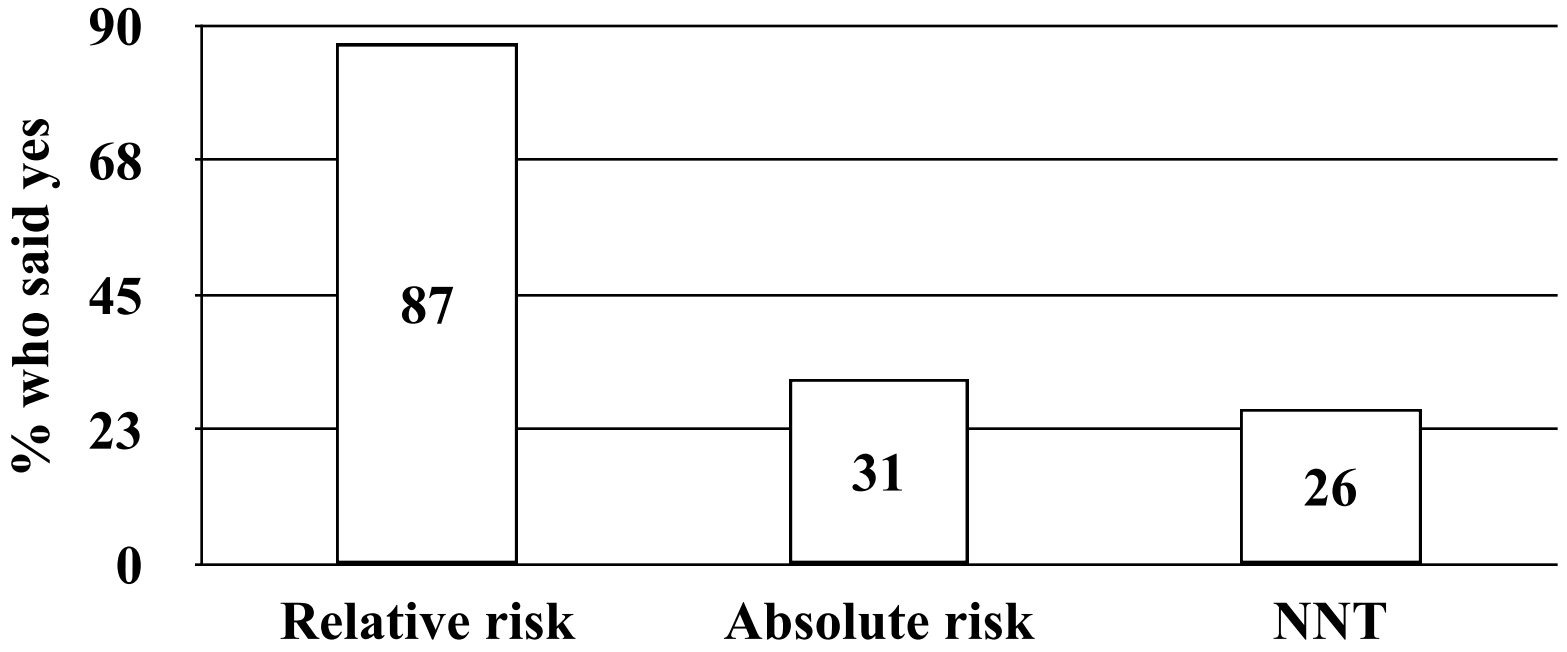
"Vasectomies increase chance of prostate cancer by 40%"

Imagine that you just found out you have a risk factor for cardiovascular disease (e.g., high blood pressure or high cholesterol).
A drug that will treat this risk factor is available and it has no side effects and its cost is covered by a plan.

Consider the following three scenarios. Would you be willing to take this drug every day for the next five years if it had been shown in a clinical trial that:

1) patients treated with this cholesterol pill had been shown to have 33% fewer heart attacks than the non-treated patients; or if
2) it was found that 2% of the patients who took this cholesterol pill had a heart attack, compared to 3% who did not take this pill – a difference of 1%; or if
3) in 100 patients who took this cholesterol pill for five years the medicine would prevent one of the 100 from having a heart attack. There is no way of knowing in advance which person that might be?

Would you take a drug daily for 5 years if it was free with no side effects



RRR = 33% fewer heart attacks
ARR = 2% of patients on this drug had a heart attack compared to 3% on placebo – a difference of 1%
NNT = Drug would prevent 1 of 100 from having a heart attack

A 33% Reduction Can Mean Events Were Reduced From:

	Absolute reduction	NNT
3/million to 2/million	1/million	1,000,000
0.3 % to 0.2 %	0.1%	1000
3 % to 2 %	1%	100
6 % to 4 %	2%	50
30 % to 20 %	10%	10
100 % to 67 %	33%	3

Benefits Must Always Be Expressed Over a Period of Time

NNT (prevent a fatal heart attack) = 300

Chew an aspirin at onset of chest pain - YES

NNT (prevent a fatal heart attack/stroke/cancer) = 1

Chew some poison hemlock now - NO

NNT (prevent a heart attack/stroke) = 50

Take a drug for 5-10 years - side effects and cost - ????

Up to

SALE - 50 % OFF

on selected items

“X” % of WHAT!!!!!!!!

Up to

SALE - 50 % OFF

on selected items

“X” % of WHAT!!!!!!!!

Statin results in patients (45-60) without cardiac disease – 5-7 years treatment

	CHD deaths (%)	All deaths (%)	Coronary events (%)
Placebo	1.4	4.1	5.0
Statins	0.9	3.7	3.3
Relative risk reduction	35	NSS	35
Absolute risk reduction	0.5		1.7
Number needed to treat	200		59

(ACAPS,WOSCOPS,AFCAPS/TexCAPS) BMJ 2000;321:983-6

Interpreting Results:

Depression trial: 200 people with MDD
x 3 months

Sadex 250 mg daily	Pharmex 200mg daily
68 people/100 are no longer depressed	48 people/100 are no longer depressed

Did this happen by chance or are they statistically different?

Interpreting Results:

Depression trial: 200 people with MDD x 3 months

Sadex 250 mg daily	Pharmex 200mg daily
50 people/100 are no longer depressed	40 people/100 are no longer depressed

$p = 0.20$

Interpreting Results:

Depression trial: 200 people with MDD
x 3 months

Sadex 250 mg daily	Pharmex 200mg daily
50 people/100 are no longer depressed	30 people/100 are no longer depressed

p value = 0.006

RRR, ARR, NNT…

$$RRR = \frac{\text{rate A} - \text{rate B}}{\text{rate A}}$$

ARR = rate A – rate B

NNT = 1/ARR

RRR, ARR, NNT…

$$RRR = \frac{50 - 30}{50} = \frac{20}{50} = 40\%$$

$$ARR = 50\% - 30\% = 20\%$$

$$NNT = 1/ARR = 5$$

Examining ARR, RRR, and NNT

Event Rate (Treatment vs. Placebo)	RRR	ARR	NNT
1% vs. 2%	50%	**1%**	**100**
10% vs. 20%	50%	**10%**	**10**
40% vs. 80%	50%	**40%**	**2.5**

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat

Important

Only calculate ARR/ARI/NNT/NNH if the result is **statistically significant**!!

NOTE: NNT and NNH

Studies have shown mixed results in terms of the usefulness of these statistics

Clinicians and patients do not always find it useful to help choose therapy

NNT of 30 may be good or bad depending on the situation

An Example: Hypoglycemia

RCT of 20 patients comparing a new diabetes treatment (drug A) vs. the control

Risk of experiencing hypoglycemia:

Drug A: 2 out of 10 pts

Risk = 2/10 = 0.2 or 20%

Control: 4 out of 10 pts

Risk = 4/10 = 0.4 or 40%

Relative Risk (RR) = risk in Drug A / risk in Control = 0.2/0.4 = 0.5

proportion of people having the event in the treatment group compared to the control group

Number Needed to Harm (NNH)

Example

Weight gain (>7kg) with olanzapine =30%

Weight gain with ziprasidone =5%

The Absolute Risk Increase (ARI)

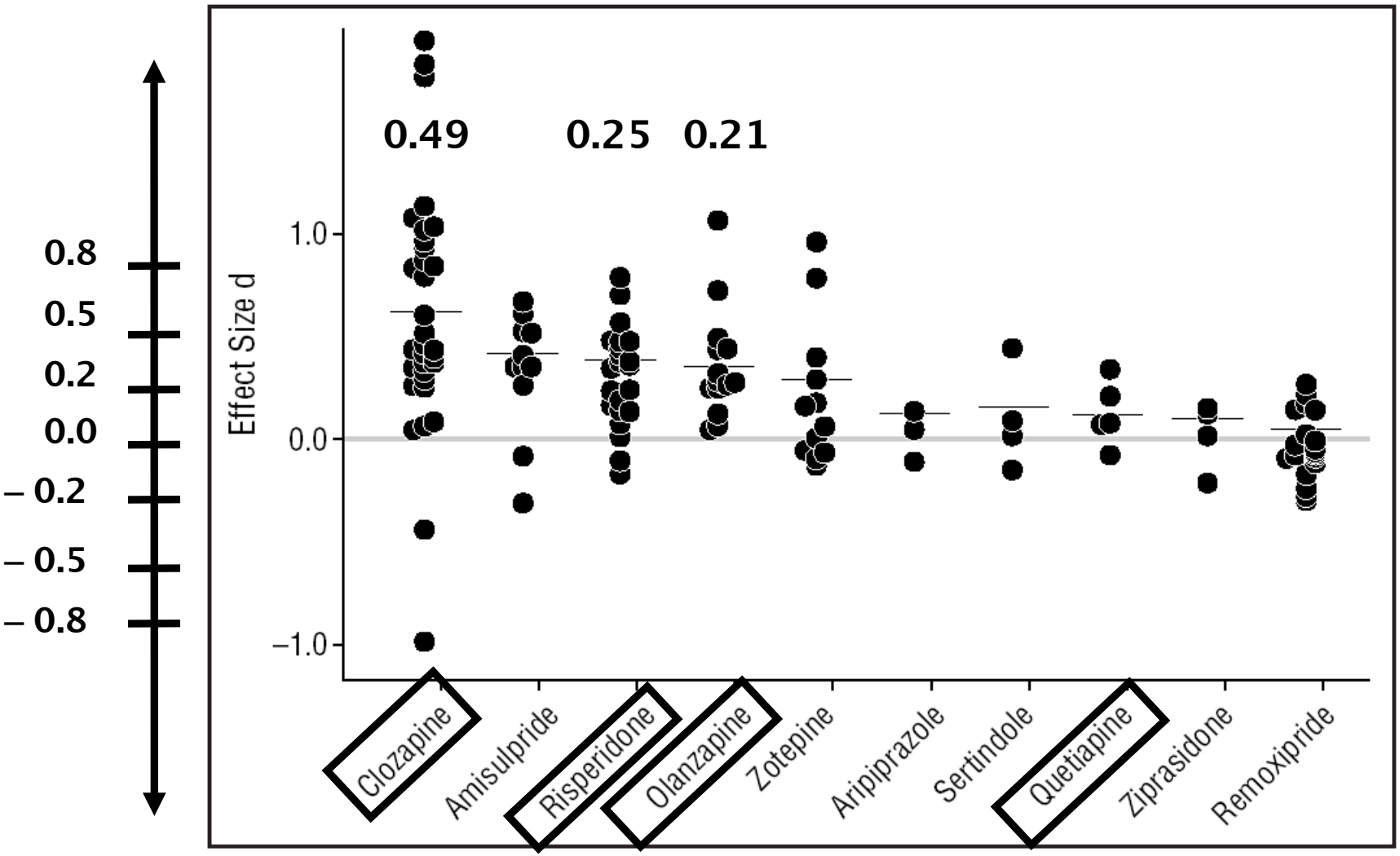
30-5=

25% increased risk with olanzapine

NNH=100/25=4

What is an effect size?

Global Symptom Improvement (Meta-analysis: Atypicals vs. Conventionals)



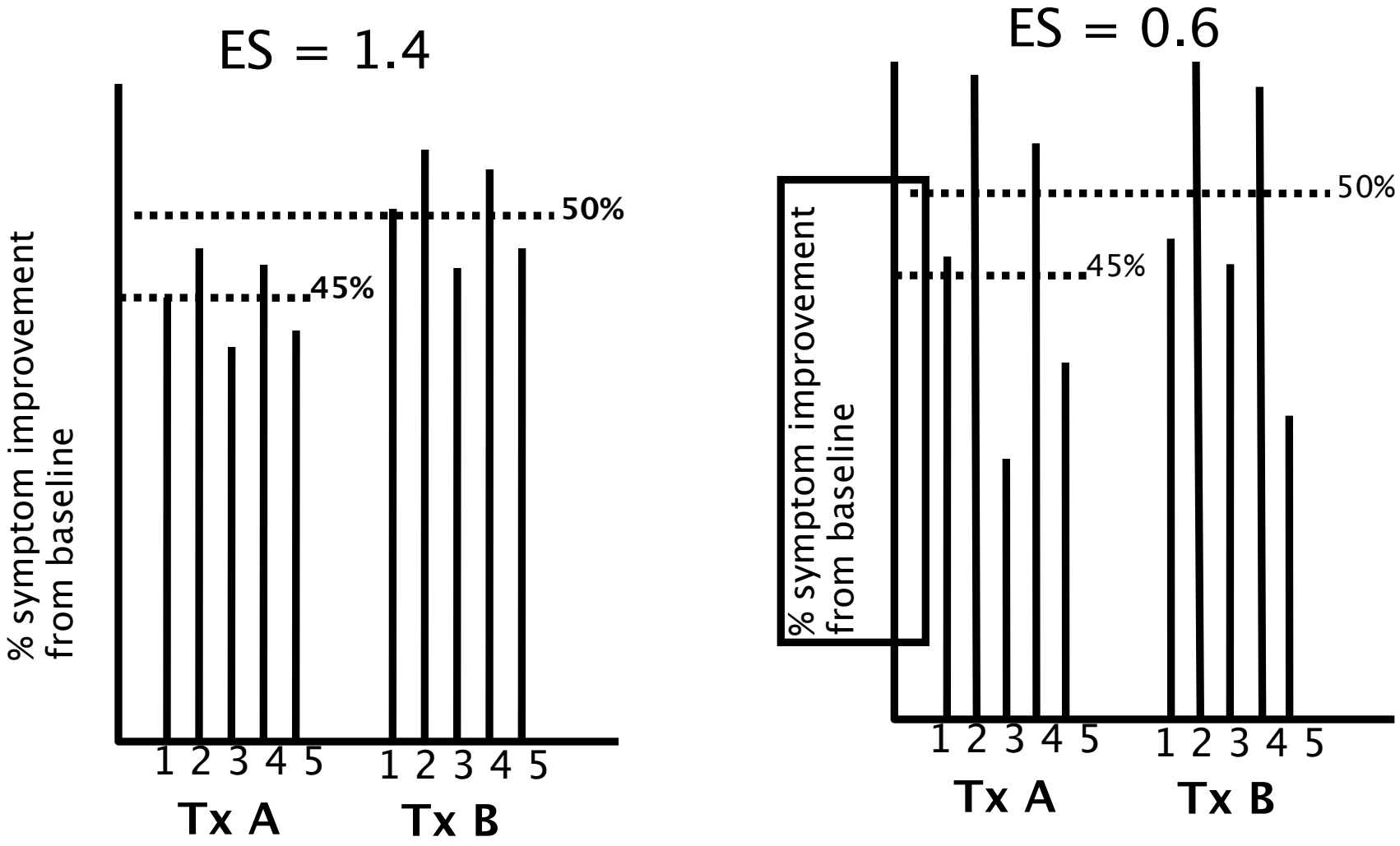
Davis et al. Arch Gen Psych 2003

N=124 trials, 18, 272 pts

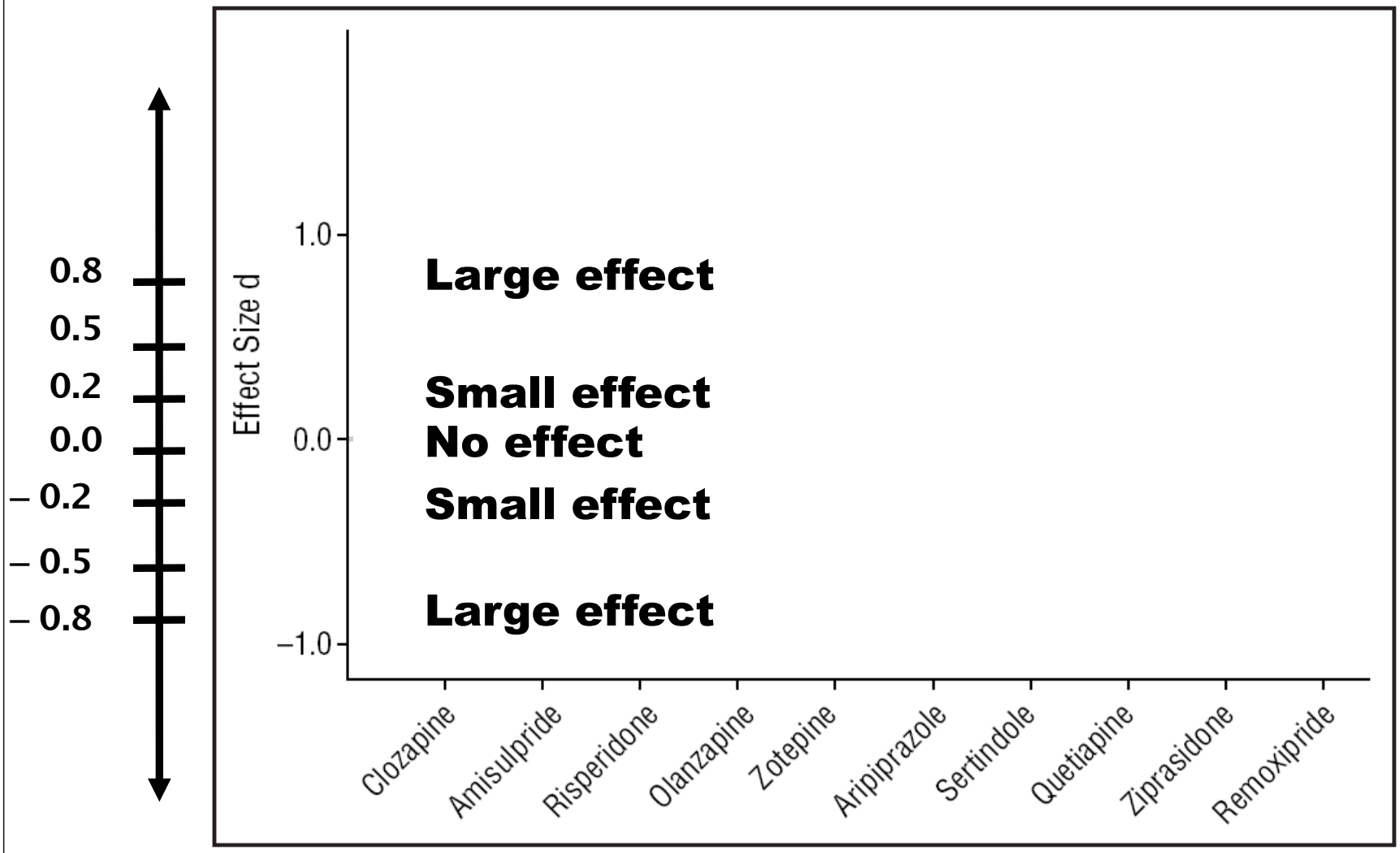
Effect size

$$ES = \frac{mean1 - mean2}{SD}$$

Illustrating Variability in



Global Symptom Improvement



Davis et al. Arch Gen Psych 2003

What is an Odds Ratio?

Commonly used in systematic reviews and epidemiological studies that list the likelihood of harm an exposure may cause

Calculated as the number of events divided by the number of non-events.

Eg, 51 boys are born in every 100 births

The odds of a randomly chosen delivery being a boy is:
(51 / 49)= 1.04

http://www.jr2.ox.ac.uk/bandolier/band25/b25-6.html

Odds Ratio (and relative risk)

Exposure/Treatment	Disease/Outcome +	Disease/Outcome -
+	a	b
-	c	d

OR = odds in the treated/exposed group divided by the odds in the control group

$$\text{Odds Ratio (OR)} = \frac{\frac{a}{b}}{\frac{c}{d}}$$

$$\text{Relative Risk (RR)} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

RR approximates OR when events are rare!