

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)

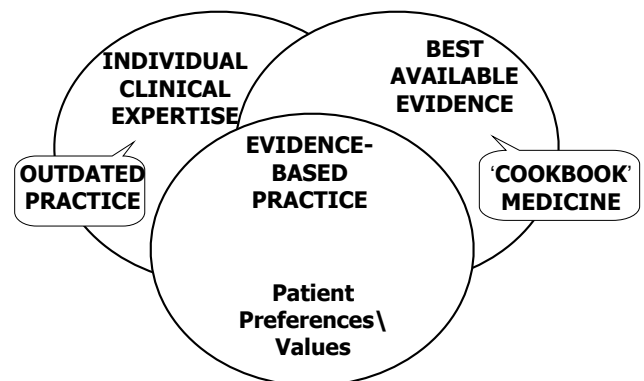
What is Evidence-Based Practice?

“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

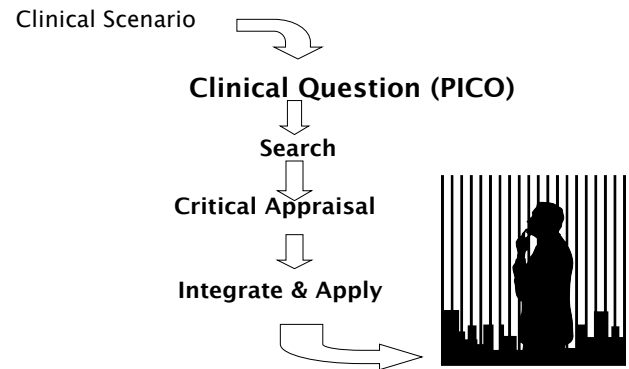
Can even be fun & make your practice more interesting

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



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

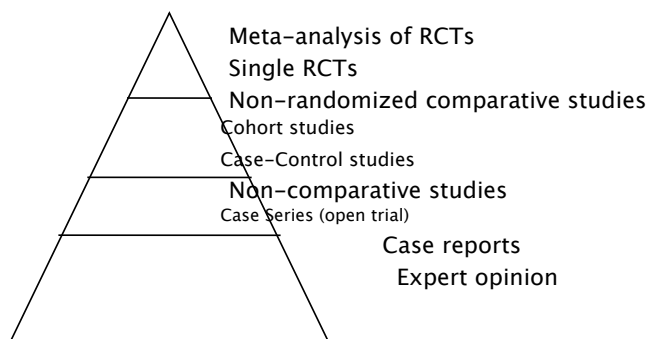
Randomized controlled trial (RCT)
Systematic review (SR)
A systematic (and hopefully rigorous) process to identify, synthesis and evaluate the available literature
Studies are:
Identified according to an explicit search strategy
Selected by defined inclusion & exclusion criteria
Evaluated against consistent 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



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 precision of the "effect estimate" from the study

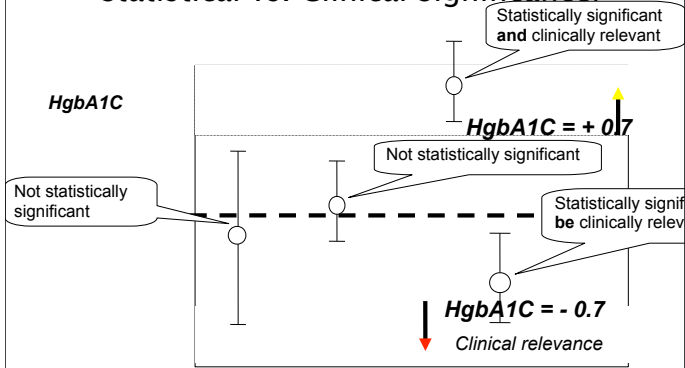
Usually reported as 95% CI

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)	Ø
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)	Ø
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%”

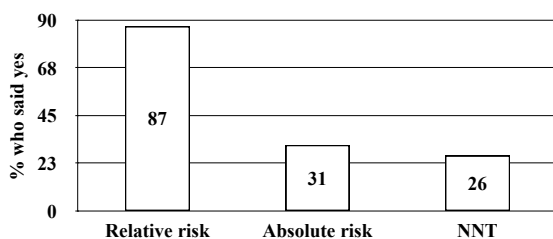
Imagine that you just found out you have a risk factor for cardiovascular disease (e.g., high blood pressure or high cholesterol).

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 – ????

SALE - 50 % OFF

“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...

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

$$\text{ARR} = \text{rate A} - \text{rate B}$$

$$\text{NNT} = 1/\text{ARR}$$

RRR, ARR, NNT...

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

$$\text{ARR} = 50\% - 30\% = 20\%$$

$$\text{NNT} = 1/\text{ARR} = 5$$

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)

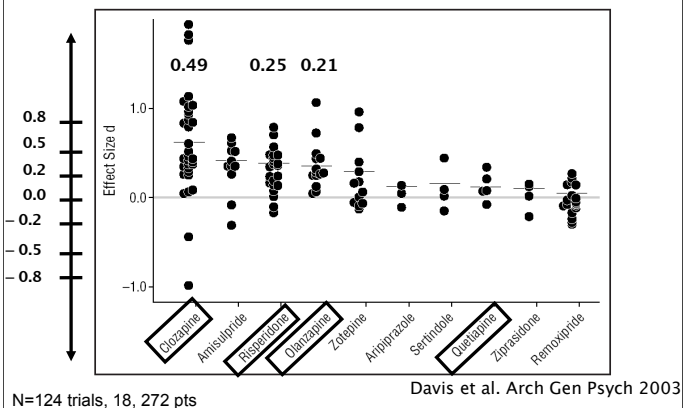
$$30 - 5 =$$

25% increased risk with olanzapine

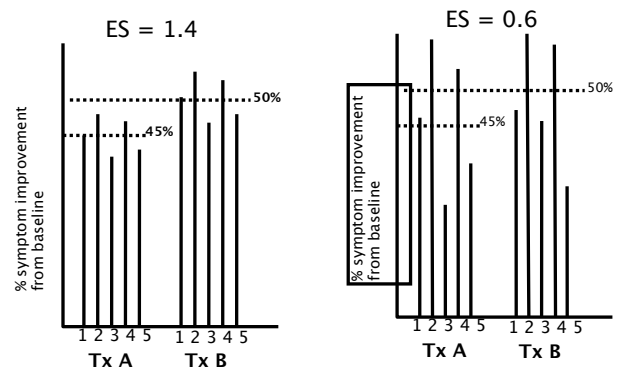
$$NNH = 100 / 25 = 4$$

What is an effect size?

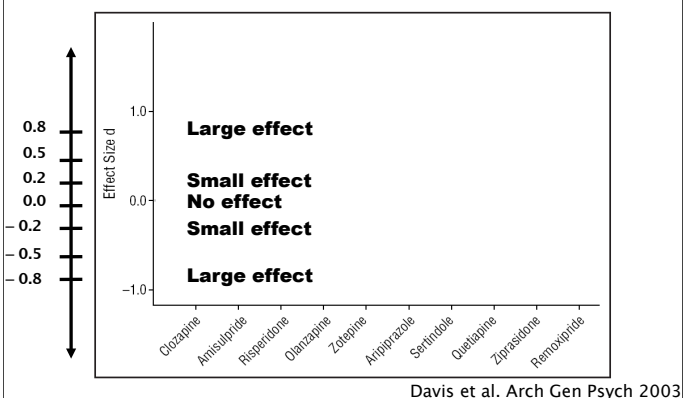
Global Symptom Improvement (Meta-analysis: Atypicals vs. Conventionals)



Effect size $ES = \frac{\text{mean1} - \text{mean2}}{SD}$ Illustrating Variability in



Global Symptom Improvement



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:

$$(51 / 49) = 1.04$$

Odds Ratio (and relative risk)

		Disease/Outcome	
		+	-
Exposure/ Treatment	+	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!

