

Zakład Medycyny Rodzinnej
Uniwersytetu Medycznego
w Łodzi

Family Medicine for English language students of Medical University of Lodz

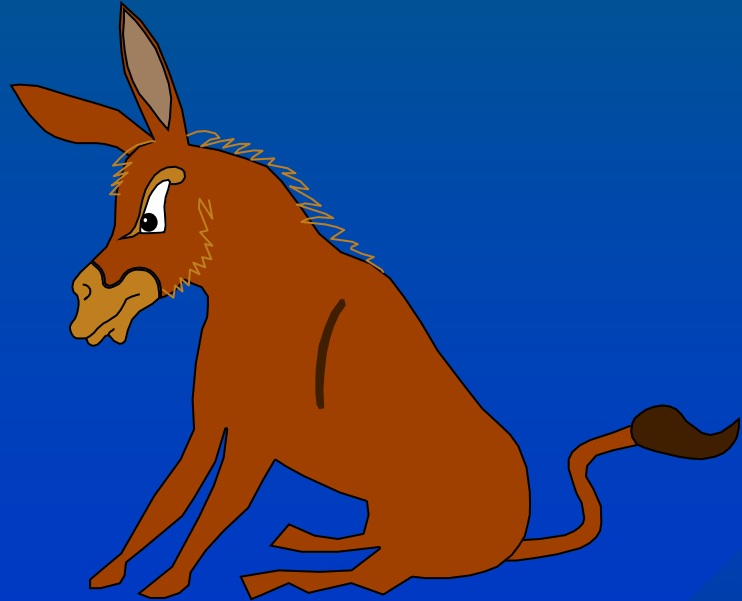
Seminary 10

Evidence based medicine

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Sources of medical decisions

- Dogma
- anecdote
- tradition
- opinion leaders



Sources of medical decisions (2)

- Mathematics:

$$e = m \cdot c^2$$

- Life sciences:

$$e = m \cdot c^2$$

(CI = 95%, $P < 0.05$)

Definition of Evidence-Based Medicine (EBM)

„Conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients; means integrating individual clinical expertise with the best available external clinical evidence from systematic research”



History of Evidence-Based Medicine (EBM)

- 1946 - first randomised trial: Bradford Hill confirmed effectiveness of streptomycin treatment in Tuberculosis
- 1990 - Evidence-Based Medicine term introduced by Gordon Guyatt, professor of medicine and clinical epidemiology in MacMaster University, Hamilton (Canada)



EBM – basics:

- Evidence-based medicine categorizes different types of clinical evidence and **rates or grades them according to the strength** of their freedom from the various biases that beset medical research.
- The **strongest evidence** for therapeutic interventions is provided by systematic review of randomized, triple-blind, placebo-controlled trials with allocation concealment and complete follow-up involving a homogeneous patient population and medical condition

Assessing the quality of evidence:

- Level I: Evidence obtained from at least one properly designed **randomized controlled trial**.
- Level II-1: Evidence obtained from **well-designed controlled trials without randomization**.
- Level II-2: Evidence obtained from **well-designed cohort or case-control** analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from **multiple time series designs with or without the intervention**.
- Level III: **Opinions of respected authorities**, based on clinical experience, descriptive studies, or reports of expert committees.

Categories of recommendations

- **Level A**: Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients.
- **Level B**: At least fair scientific evidence suggests that the benefits of the clinical service outweighs the potential risks. Clinicians should discuss the service with eligible patients.
- **Level C**: At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations.
- **Level D**: At least fair scientific evidence suggests that the risks of the clinical service outweighs potential benefits. Clinicians should not routinely offer the service to asymptomatic patients.
- **Level I**: Scientific evidence is lacking, of poor quality, or conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

Steps of Evidence-Based Medicine

1. **Formulate the question** (population, intervention, comparison intervention, outcomes, time horizon, setting)
2. **Search the literature** to identify studies that inform the question
3. **Interpret each study** to determine precisely what it says about the question; if several studies address the question, synthesize their results
4. **Summarize the evidence** in „evidence tables“; compare the benefits, harms and costs in a „balance sheet“; draw a conclusion about the preferred practice
5. Applying the information in clinical practice

Example of good guidelines

Recommendations

6.2.1. In patients with bioprosthetic valves who have AF, we recommend long-term treatment with vitamin K antagonists with a target INR of 2.5 (range, 2.0 to 3.0) [**Grade 1C**].

6.2.2. For patients with bioprosthetic valves who are in sinus rhythm and do not have AF, we recommend longterm therapy with aspirin, 75 to 100 mg/d (**Grade 1C**).

Example of good guidelines

Table 1—Current Approach to Grades of Recommendations*

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	RCTs without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws†)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

Effectiveness of clinical guidelines

Tabela 1. Leki otrzymywane przez pacjentów z chorobą wieńcową przy wypisie ze szpitala w USA i Europie

Lek	U.S. Medicare ⁵ (2000-2001)	Euro Heart Survey ⁶ (2000-2001)	GRACE ⁷ (1999-2000)	GWTG ⁸ (2001-2002)
Kwas acetylosalicylowy	86%	89%	89%	93%
Beta-adrenolityk	79%	75%	71%	79%
Inhibitor ACE	74%	61%	55%	64%
Statyna	40%	54%	47%	66%
Populacja	AMI	STEMI	OZW	CAD

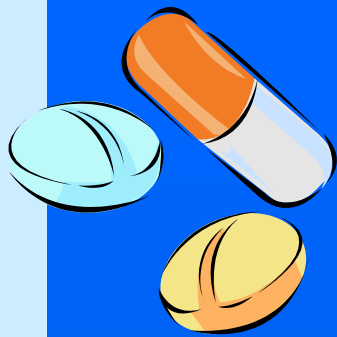
Pros and cons of evidence based medicine

Positives of EBM

-
-
-

Negatives of EBM

-
-
-

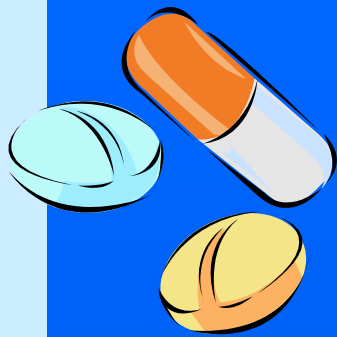


Evidence based medicine limitations

Therapeutic decisions are frequently relied on trial results.

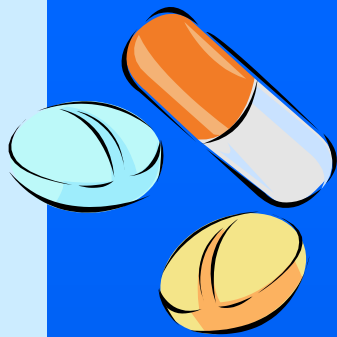
But:

- results of the trials performed in highly selected populations should not be extrapolated
- a number of normal patients would be excluded from most of the trials
- the drug that was beneficial within the trial, may be less effective in particular patient (due to individual organism's reaction), and even improper (due to side effects)



Evidence based medicine limitations (2)

- papers in peer-reviewed journals are more likely to contain positive findings if the research is funded by industry
- among the authors of original research papers, reviews and letters to the editor that were supportive of the drugs' use, 96% had financial relationships with the drugs' manufacturers; for publications deemed neutral or critical the figure was only 60% and 37% respectively
- negative results are either de-emphasised or simply not published



Evidence based medicine limitations (3)

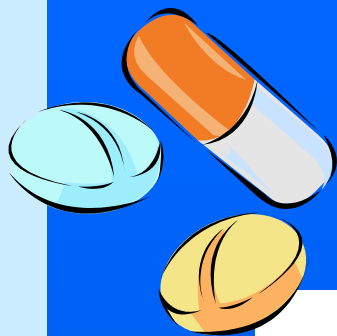
- clinical trials are very expensive
- far more clinical trials have been conducted on pharmaceutical products than on alternative therapies
- absence of evidence is not evidence of absence of effect



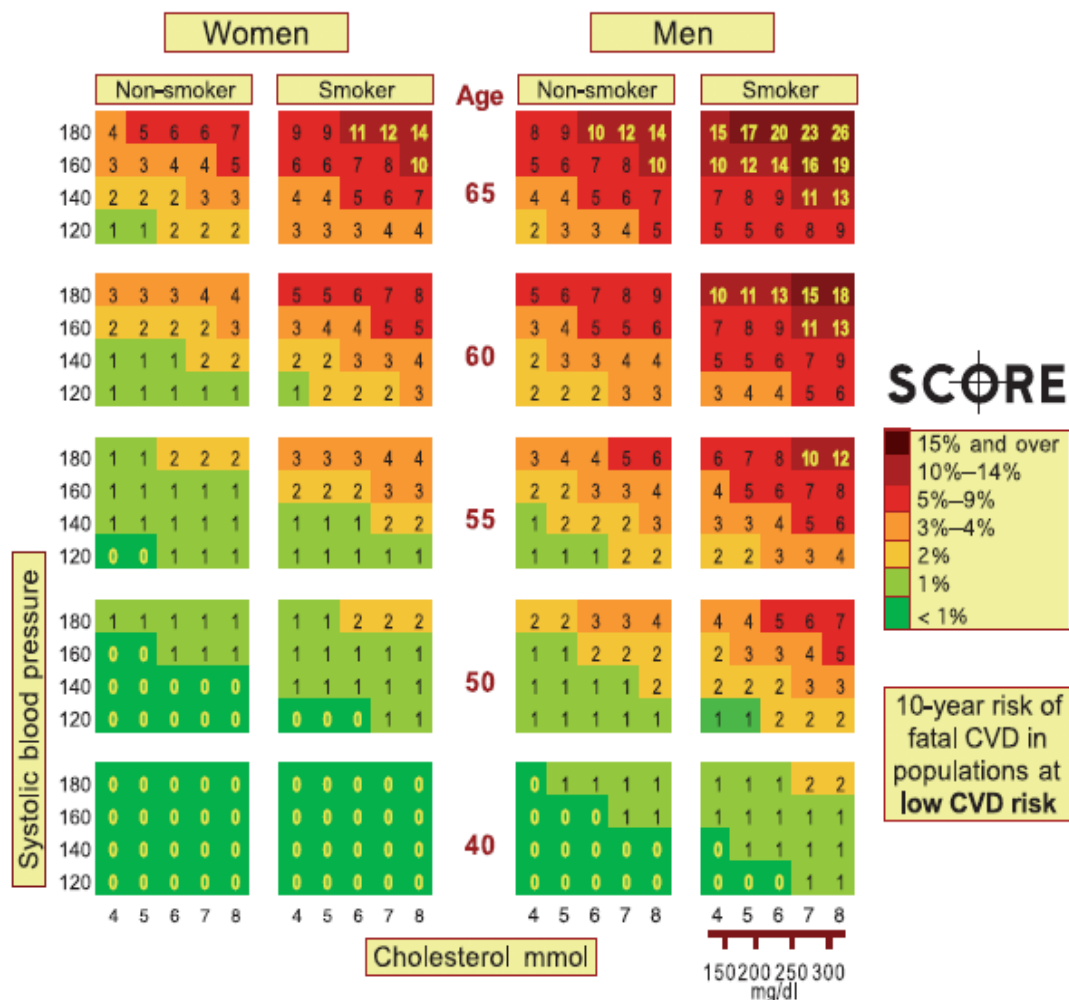
Doctor's concerns about guidelines

Opinion of 1199 Italian doctors about antibiotic guidelines:

- Guidelines are perceived to be less useful than the other sources of medical information (e.g. personal experience, conferences, colleagues, articles, the Internet, and textbooks)
- developed for cost-containment reasons?
- Have limited applicability to individual patients and local settings



EBM and its role in taking medical decisions



Ten-year risk of fatal cardiovascular disease in populations at low cardiovascular disease risk (according to the SCORE study).

EBM and sources of medical information

- Original papers
- Reviews
 - systematic reviews
 - meta-analyses
- Textbooks
- Lectures
- opinion leaders
- Pharmaceutical representatives
- Clinical guidelines
- Clinical experience

Sources of medical information

The Cochrane Collaboration - Microsoft Internet Explorer

Wstecz Dalej Zatrzymaj Odśwież Start Wyszukaj Ulubione Multimedia Historia Poczta Drukuj Edytuj

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From the newsroom

The Cochrane

<http://www.thecochranelibrary.com/> Internet

Sources of medical information

The screenshot displays the Entrez PubMed web interface within a browser window titled "Entrez PubMed - Neostrada TP". The browser's address bar shows the URL: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pubmed>. The PubMed logo and tagline "A service of the National Library of Medicine and the National Institutes of Health" are visible at the top. The search bar contains the text "sexual abuse", and the results show "All: 13661" items. The first three results are listed below:

- ☐ 1: [Kirkcaldy BD, Siefen GR, Urkin J, Merrick J.](#) Related Articles, Links
Risk factors for suicidal behavior in adolescent.
Minerva Pediatr. 2006 Oct;58(5):443-50.
PMID: 17008855 [PubMed - in process]
- ☐ 2: [Tucker W, Olsson M, Simring S, Goodman W, Bienenfeld S.](#) Related Articles, Links
A pilot survey of inmate preferences for on-site, visiting consultant, and telemedicine psychiatric services.
CNS Spectr. 2006 Oct;11(10):783-7.
PMID: 17008821 [PubMed - in process]
- ☐ 3: [Jewkes R, Dunkle K, Nduna M, Levin J, Jama N, Khuzwayo N, Koss M, Puren A, Duvvury N.](#) Related Articles, Links
Factors associated with HIV sero-status in young rural South African women: connections between intimate partner violence and HIV.
Int J Epidemiol. 2006 Sep 28; [Epub ahead of print]
PMID: 17008362 [PubMed - as supplied by publisher]

The interface also includes navigation tabs for "All Databases", "PubMed", "Nucleotide", "Protein", "Genome", "Structure", "OMIM", "PMC", "Journals", and "Books". A left sidebar provides links to "About Entrez", "Text Version", and "Entrez PubMed" services. The bottom of the image shows a Windows taskbar with various open applications and the system clock at 00:30.

Confidence Intervals and P Values

- **The P value** tells us how likely it is that the difference between groups occurred by chance rather than because of an effect of treatment. For example, if the absolute risk reduction was 4% with $P = .04$, if the study were done 100 times, the risk reduction would be expected to be caused four times by chance alone.
- **The confidence interval (CI)** gives a range and is more clinically useful. A 95% confidence interval indicates that if the study were repeated 100 times, the study results would fall within this interval 95 times. For example, if a study found that a test was 80% specific with a 95% confidence interval of 74% to 85%, the specificity would fall between 74% and 85% 95 times if the study were repeated 100 times.

Likelihood Ratios

- A test with an LR of 1.0 indicates that it does not change the probability of disease. The higher above 1 the LR is, the better it rules in disease (an LR greater than 10 is considered good). Conversely, the lower the LR is below 1, the better the test result rules out disease (an LR less than 0.1 is considered good).

ARR – absolute risk reduction

RRR – relative risk reduction

- For example, if mortality is 20% in the control group and 10% in the treatment group, there is a 50% **relative risk reduction** $([20 - 10] \div 20) \times 100\%$. However, if mortality is 2% in the control group and 1% in the treatment group, this also indicates a 50% relative risk reduction, although it is a different clinical scenario.
- **Absolute risk reduction** subtracts the event rates in the control and treatment groups. In the first example, the absolute risk reduction is 10%, and in the second example it is 1%. Reporting absolute risk reduction is a less dramatic but more clinically meaningful way to convey results.

True positive/false negative

- **True positive**: Sick people correctly identified as sick
- **False positive**: Healthy people incorrectly identified as sick
- **True negative**: Healthy people correctly identified as healthy
- **False negative**: Sick people incorrectly identified as healthy

Sensitivity and Specificity

- **Sensitivity** is the percentage of patients with a disease who have a positive test for the disease in question
- **Specificity** is the percentage of patients without the disease who have a negative test

		Patients with bowel cancer (as confirmed on endoscopy)		
		Condition positive	Condition negative	
Fecal occult blood screen test outcome	Test outcome positive	True positive (TP) = 20	False positive (FP) = 180	Positive predictive value = $TP / (TP + FP)$ = $20 / (20 + 180)$ = 10%
	Test outcome negative	False negative (FN) = 10	True negative (TN) = 1820	Negative predictive value = $TN / (FN + TN)$ = $1820 / (10 + 1820)$ ≈ 99.5%
		Sensitivity = $TP / (TP + FN)$ = $20 / (20 + 10)$ ≈ 67%	Specificity = $TN / (FP + TN)$ = $1820 / (180 + 1820)$ = 91%	

Number Needed to Treat Number Needed to Harm

- The NNT is the average number of patients who need to be treated to prevent one additional bad outcome (e.g. the number of patients that need to be treated for one to benefit compared with a control in a clinical trial). It is defined as the inverse of the absolute risk reduction.
- $NNT=1$ means that all patients who are given a specific treatment will be cured

EBM glossary

- **randomized trial**
- **crossover study**
- **parallel study.**
- **single-blind study**
- **double-blind study**
- **triple-blind study**
- **systematic review**
- **end-point**

Crossover study

- A **crossover study**, also referred to as a **crossover trial**, is a study in which subjects receive a sequence of different treatments (or exposures).
- In most crossover trials, each subject receives all treatments.
- Advantages: the influence of confounding covariates is reduced because each crossover patient serves as his or her own control; optimal crossover designs are statistically efficient and so require fewer subjects than do non-crossover designs;
- Limitations/disadvantages: it is possible that the order in which treatments are administered may affect the outcome; the issue of "carry-over" between treatments, which confounds the estimates of the treatment effects;

Clinical endpoint

- The **primary endpoint** of a clinical trial is the endpoint for which subjects are randomized and for which the trial is powered.
- **Secondary endpoints** are endpoints that are analyzed *post hoc*, for which the trial may not be powered nor randomized.
- Examples (as far as oncology goes) include discovery of local recurrence, discovery of regional metastasis, discovery of distant metastasis, onset of symptoms, hospitalization, increase or decrease in pain medication requirement, onset of toxicity, death from cancer itself or from any cause.

Sources:

- Essentials of Family Medicine [ed. P.D.Sloane et al]; 6th Edition
- <http://www.aafp.org/journals/afp/authors/ebm-toolkit/glossary.html>
- <http://www.consort-statement.org/resources/glossary>
- www.wikipedia.en (EBM glossary)