

# Incorporating Evidence-Based Medicine into Clinical Practice: Practical Tools for Information Mastery

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# Overall Session Format

- Brief Introduction
- EBM into Clinical Practice
- Practical Tools Interactive Session
- Question and Answer

# Session Objectives

- Define the concept of information mastery and discuss its role in applying new information in practice
- Evaluate a research study case example for validity and relevance to support drug therapy decision making

# Why Talk About EBM?

- “The strength of a profession lies in its expert generation of information and better management of it than other social groups” EJ Huth
- “The illiterate of the 21<sup>st</sup> century are not those who can't read or write but those who cannot learn, unlearn, and re-learn” Alvin Toffler
- ACPE, AACCP, ASHP, APhA, ACCP, IOM, and all health professions place an emphasis on ability to provide evidence-based care

# Expectations of Graduates

- Self directed life long learner: independence
- Use best evidence for therapeutic recommendations
- Be prepared to answer the question “why do you recommend that?”
- Maintain current awareness
- Lead and teach others to make the best use of medications

# Evidence Based Medicine

- Definition: “The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” Sackett 1996
- The practice of evidence based medicine requires the integration of individual clinical expertise, judgment and patient choice with the best external evidence from systematic research

# Information Mastery

- Allen Shaughnessy and David Slawson
- Feeling good about not knowing everything
- Emphasis on information usefulness
- POEM over DOE
- Medical chatter, gossip, ping pong, jazz
- YODA -your own data appraiser
- Probability statement- what we do for patients does more good than harm



# It's a Jungle Out There!

- New information available daily
- The public has a high interest and demand
- Goal: Get in, get where and what you want, and get out quickly



# Old Model for Clinical Decisions

- Unsystematic observations/clinical experience
- Pathophysiology plus pharmacology
- Extrapolation from intermediate outcomes
- Authority of local experts
- Practitioners and patients not “equals”

# New Model for Clinical Decisions

- Systematic recording of observations - reproducible and unbiased
- Mechanism of disease - necessary but not sufficient
- Critical literature appraisal Vs authority
- Apply rules of evidence
- Full informed participation by patients

# The Practice of “EBM”

- A process of life-long, self directed learning in which caring for our patients creates the need for clinically important information about diagnosis, prognosis, prevention, therapy, and other clinical and health care related issues
- Information management is critical (generate, collect, store, retrieve, analyze, synthesize, apply evidence)

# The Practice of “EBM”

- Convert information needs into answerable questions
- Track down the best evidence to answer these questions
- Critically appraise that evidence for validity and applicability or usefulness
- Apply the results of this appraisal in our clinical practice
- Evaluate our performance

# Ask Answerable Questions

- Directly relevant to the patients problem and structured in a way to direct a search for evidence (PICO)
- Describe the Patient (age, sex, problem list, severity of illness, risk factors)
- Identify a potential Intervention (therapy)
- Identify possible Comparative intervention (may include observation only)
- Define the Outcome desired

# Patient Oriented Evidence that Matters

- Clearly defined population
- Population comparable to your patients
- Intervention well described and doable
- Outcome of importance to patients
- Information usefulness =

relevance x validity

work

# POEM Outcomes

- This
  - mortality
  - hospitalization
  - morbidity
  - quality of life
  - patient satisfaction
- Not This
  - lab test change
  - physiologic measure
  - intermediate outcome
  - pharmacokinetics

# EBM Criticisms

- Shortage of “good” evidence (grey zones)
- Applying evidence to individual patient
- Resources, time, administrative barriers
- Need to develop new skills (search, appraise)
- Where is the evidence that EBM works?

# EBM is NOT

- Cookbook medicine- must use clinical expertise, judgment, patient choice
- Old hat- note evidence for variations and underuse of effective care and continued use of ineffective or poor care
- Impossible to practice- McMaster, Oxford and other examples

# EBM is NOT

- Just cost cutting- applying most efficacious interventions will increase efficiency but may also increase total expenses
- Restricted just to RCT and meta-analysis

# EBM Why Bother?

- New evidence is generated at a rapid rate which should change our practice
- Although we need the evidence, most practitioners currently don't obtain it
- Our knowledge and performance will deteriorate rapidly without EBM
- Traditional CE programs have not been effective in improving performance
- EBM has been shown to keep practitioners up to date

# 6S Hierarchy of Pre-appraised Evidence

- Systems – computerized decision support
- Summaries- EB clinical practice guidelines, PIER, UpToDate, Dynamed, Essential Evidence Plus,
- Synopses of Synthesis- DARE, AHRQ, NICE

6S-R Brian Haynes McMaster University

## 6S Hierarchy of Pre-appraised Evidence

- Synthesis- systematic reviews in journals, Cochrane, AHRQ, others
- Synopses of Studies- ACP journal club, McMaster PLUS, others
- Studies- original articles, Medline, IDIS, etc

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# Evolution of EBM Information

- Pre-EBM: Passive diffusion (“publish it and they will come”)
- Early EBM: Pull diffusion (“teach them to read it and they will come”)
- Current EBM: Push diffusion (“read it for them and send it to them”)
- Future EBM: Prompt diffusion (“read it for them, connect it to their individual patients”)

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# Purpose of Literature Evaluation

- Establish cause/effect relationship
- Predict outcomes for subsets or individuals
- Estimate the size / frequency of treatment effects
- Balance risk/benefit of therapy
- Extrapolate from study results to populations or particularize to individual
- Understand the whole story, perspective
- Self directed learning and evidence-based practice

# Steps in Literature Evaluation

- Be selective in studies to evaluate
- Identify the study hypothesis
- Identify the basic trial design
- Identify additional questions that need to be answered to assess validity
  - all factors related to the patients, interventions, outcomes
  - compliance with the protocol
  - statistical methods and analysis

# Criteria to Select an Article to Read

- Published in a “high impact” journal
- Topic of interest based on the title
- Likely to be applicable to your practice setting based on topic and patients
- Measured outcomes that are important
- Methods likely to produce valid results
- Authors are recognized experts
- Perform the “so what” test

# Causes of the Effect

- Drug therapy studies common goal; ultimately to define (and quantitate) cause/effect relationships to predict benefits and risks of treatment options
- Potential causes of an effect include:
  - Treatment (independent variable, risk factor of interest)
  - Random error (chance)
  - Systematic error i.e. bias
    - Confounding variables

# Causality Assessment

- Consistent with existing information
- Reproducible
- Time sequence
- Specificity of association
- Strength of association
  - Quantitative
  - Dose-response
  - Study design

# Sources of bias

- Selection bias- systematic differences in comparison groups
- Performance bias- systematic difference in the care provided other than the treatment or control
- Attrition bias- systematic differences in withdrawals
- Detection bias- systematic differences in outcome assessment

# Levels of Evidence in Therapy Questions

Most Valid

- Confirmed randomized controlled trials, meta-analysis



- RCTs- narrow CI, with low false positive ( $\alpha$ ) and low false negative ( $\beta$ ) errors

- RCTs - wide CI, size of effect not clinically significant, false negative results, heterogeneity present

- Non-randomized prospective cohort study

- Non-randomized historical case-control study

- Case series without control subjects

Least Valid

- Expert opinion

# Statistics for Nonstatisticians

- I am a user of statistics, not a statistician (although it is nice to have friends who are)
- Statistic- measurement that describes a sample
- You need to understand both descriptive and analytical statistics
- Understand the size of the treatment difference as well as the probability that a difference exists

# Statistics for Dichotomous Results

- Incidence
- Prevalence
- Relative risk
- Hazard ratio
- Odds ratio
- Relative risk reduction
- Absolute risk reduction
- Number needed to treat

# Interpretation of Relative Risk

- If the number is  $> 1$  the risk of that event (or disease) is greater if the intervention (or risk factor) is present than if it is absent.
- If the number is  $< 1$  the risk of that event is less if the intervention (or risk factor) is present.
- So what if the Relative Risk = 1 ?

# Confidence Intervals

- Combines information about the strength of an association (effect size) and the statistical significance (effects of chance) of the result
- 95% CI is commonly used
  - 95% of all samples would give a result within the ranged specific by the CI
- For RR the value of 1 represents no difference between groups (no effect of treatment) i.e. If the 95% CI of the OR or RR includes 1, the result is not statistically significant

# Examples of RR with 95% CI

	Relative Risk	95% Confidence Interval
A	1.6	0.8 – 2.4
B	1.6	1.2 – 2.0
C	0.8	0.6 – 1.4
D	0.8	0.5 – 0.9

# Case Example

- MUCOSA trial. Silverstein FE Ann Intern Med 1995;123:241-249
- Patient oriented evidence that matters (POEM)
- How to look at the results, relative risk reduction, absolute risk reduction, number needed to treat
- Importance of baseline risk
- Quantitate benefits and risk for individual patients

# MUCOSA Results

- Relative Risk  $\frac{25/4404^*}{42/4439} = 0.60$ 
  - 95% confidence interval of RR was 0.36-0.98
- Relative Risk Reduction = .4 = 40%
- Absolute Risk Reduction = 0.0038
- Number needed to treat (NNT) for 6 months to prevent one ulcer complication  
 $1/0.0038 = 263$

\*There were 25 ulcer complications in the treated group of 4404, and 42 complications in the control group of 4439

# Adjust Estimate of Benefit for an Individual Patient

$$\frac{\text{CER}}{\text{PEER}} \times \text{NNT} \quad \text{or} \quad \frac{1}{\text{PEER} \times \text{RRR}}$$

Risk Factors	Event Rate (%)	NNT
0	0.38	657
1	0.87	287
2	1.95	128
3	4.32	58
4	9.24	27

# It is All In How You Look at It

- Suppose A:      event rate treated 0.6%  
                      event rate control 0.9%  

Relative risk reduction = 33%
- Suppose B:      event rate treated 6%  
                      event rate control 9%  

Relative risk reduction = 33%
- However:
  - absolute risk reduction in A is 0.3% so NNT is 333
  - absolute risk reduction in B is 3% so NNT is 33

# Types of Errors of Significance Test

- Type I: Reject the null when it is true
  - say there was an effect when there is actually not
  - usual accepted value of this (alpha) is 0.05
- Type II: Accept the null when it is false
  - say there is no difference when there actually is
  - accepted value (beta) not as standard, typical is between 0.10 and 0.20 but many studies fail
- Power is 1 minus beta:
  - With a beta of 0.10 you have a 90% chance to detect a difference (of a specified size) if it exists

# Sample Size and Power

- The greater the sample size the greater the power
- Sample size calculated based on:
  - Accepted alpha (usually 0.05)
  - Accepted beta (0.1 to 0.2)
  - Size of treatment difference you want to detect (referred to as delta)
  - Measure of variability (SD) for continuous data
  - Rate of events in control patients for dichotomous data

# P Values are not Magic

- Statistical significance by itself means little
- Weigh against practical concerns
  - what is the size of benefit
  - how does it compare to alternatives
  - what is the CI or other measure of precision
  - what are the relative toxicities
  - cost

# Interactive Exercise

- ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-85
- Trial design, participants, interventions, outcomes, sample size, randomization, blinding, results, completeness of follow-up, generalisability, balance of benefit/ harm, recommendation for practice

# Tools in Practice

- ASHP, ACCP, APhA, AACCP, AMCP, etc
- FDA – news, recalls, alerts, shortages, new drug approval, labeling, approval package, advisory committee reports
- Email alters and list servers/other
  - <http://www.acpjc.org/>, EvidenceAlerts@STATRef.com, MacPlusFS [macplus@mcmasterhkr.com], CardioExchange, CardioBrief, DailyDose@ModernHealthcare.com, Medscape, docguide, essentialevidenceplus, <http://www.aafp.org/online/en/home/publications/journals/afp/ebmtoolkit.html>

# Self-Study Resources

- <http://www.consort-statement.org/>
  - Checklist and flow diagram
  - Explanation and Elaboration Document
  - Extensions for design e.g. non-inferiority, pragmatic, articles about harm
  - Other related guidelines and initiatives
- <http://www.prisma-statement.org/>
  - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
  - Checklist and flow diagram

# Self-Study Resources

- <http://www.cochrane.org/>
  - <http://www.cochrane.org/training>
  - <http://www.cochrane.org/training/cochrane-handbook>
- <http://www.jamaevidence.com/>
  - Users' Guides to the Medical Literature
- <http://ktclearinghouse.ca/cebm>
  - Evidence-based Medicine: How to Practice and Teach EBM
  - Intro to EBM, resource lists, tools,

# Self-Study Resources

- <http://www.cebm.net/>
  - University of Oxford- Publications, training, tools, resource center, workshop videos, calculators
- The AGREE II Instrument Appraisal of Guidelines for Research and Evaluation
  - <http://www.agreetrust.org/home/>
- GRADE Grading of Recommendations Assessment, Development and Evaluation
  - <http://www.gradeworkinggroup.org/> Toolbox, publications, links to SIGN, NZGG, G-I-N, NICE

# Self-Study Resources

- The Health Information Research Unit (HIRU) in the Clinical Epidemiology and Biostatistics Department at McMaster University <http://hiru.mcmaster.ca/hiru/>
  - McMaster **H**ealth **K**nowledge **R**efinery (HKR) [http://hiru.mcmaster.ca/hiru/HIRU\\_McMaster\\_HKR.aspx](http://hiru.mcmaster.ca/hiru/HIRU_McMaster_HKR.aspx)
  - McMaster PLUS [http://hiru.mcmaster.ca/hiru/HIRU\\_McMaster\\_PLUS\\_projects.aspx](http://hiru.mcmaster.ca/hiru/HIRU_McMaster_PLUS_projects.aspx)

# Self-Study Resources

- <http://www.ahrq.gov/clinic/>
  - Evidence-based Practice, Clinical Practice Guidelines, USPSTF,
  - Effective Health Care  
<http://effectivehealthcare.ahrq.gov/>  
Comparative Effectiveness Research
    - Methodology issues
    - Guides, Reviews, Reports

# Self-Study Resources

- Drug Information: A Guide for Pharmacists. Patrick Malone, Karen Kier, John Stanovich
- Designing Clinical Research. Stephen B Hulley, Steven R Cummings, et al
- The Pharmacist's Guide to Evidence Based Medicine for Clinical Decision Making. Patrick J Bryant, Heather A Pace
- Studying a Study and Testing a Test: How to Read the Medical Evidence. Richard K.

# Three last thoughts

- “All the science in the world has no effect until it is implemented properly, and measuring performance is one of the most powerful tools for implementation” David Eddy
- “It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials”  
Archie Cochrane
- “The one real objective of education is to leave a person in the condition of continually asking questions” Bishop Creighton

# Questions?

