Evidence-Based Medicine versus Personalized Medicine: Are They Enemies? (03/06/16)

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Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Appreciate the concept of statistical heterogeneity.
2. Understand the relationship between statistical heterogeneity and evidence-based medicine.
3. Understand the relationship between statistical heterogeneity and personalized medicine.
4. Be aware that evidence-based medicine and personalized medicine have conflicting approaches.

Fantastic Objective

At the conclusion of this presentation, the participant should be developing a “craving” to read the editorial “Evidence-based medicine versus personalized medicine: are they enemies? *Journal of Clinical Psychopharmacology* 32(2):153-164, 2012.”

http://www.ncbi.nlm.nih.gov/pubmed/22367661

Pre-published free version:

http://uknowledge.uky.edu/psychiatry_facpub/41/

Acknowledgements

1) This presentation is a naïve attempt to teach complex concepts. Learning them is necessarily an active process. You can learn complex concepts but I cannot teach you complex concepts without your effort to learn them.

2) I am grateful to one of the editors of the *Journal of Clinical Psychopharmacology* and the reviewers who "forced" me to further review the literature, sharpen my thinking and asked me to provide solutions for the problem.

Abbreviations

- ADR: adverse drug reaction
- CME: continuing medical education
- CNV: copy number variations
- CYP: cytochrome P450
- EBM: evidence-based medicine
- FDA: Food and Drug Administration
- m±SD: mean±standard deviation
- NNT: number needed to treat
- P_{25}, P_{50}, P_{75}: percentiles 25, 50 and 75
  P_{25} is the value (or score) below which 25 percent of the observations may be found.
- PM: personalized medicine (in this presentation)
- RCT: randomized controlled trial
- TCA: tricyclic antidepressant

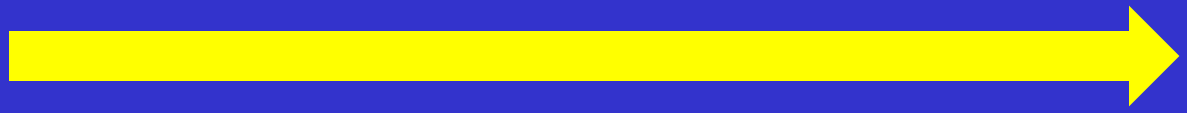
Warning For Haters of Statistics

- If you hate "Statistics":
  - You may want to jump over these more complicated sections:
    - 3.2.3. on Limitations of the Scientific Approach in Medicine
    - 3.3. on EBM's Relationship with Statistical Heterogeneity
    - 4.3. on PM's Relationship with Statistical Heterogeneity
- If you are unable to grasp:
  - what statistical heterogeneity is, and
  - that statistical heterogeneity is the main problem for EBM and RCTs,

you should fire Dr. de Leon as your teacher in psychopharmacology.

Types of RCTs

- Parallel RCTs: patients are randomized to:

  Treatment A 

  Placebo 

- Cross-over RCTs: patients are randomized to:

  Treatment A  Placebo

  Placebo  Treatment A

Genetic Concepts

- Epigenesis: A genetic process by which the adult organism is realized via mechanisms that lead to the restriction in the possible fates of cells, eventually leading to their differentiated state. Mechanisms involved cause **heritable changes** to cells **without changes to DNA sequence** such as
  - DNA METHYLATION;
  - HISTONE modification;
  - DNA REPLICATION TIMING;
  - NUCLEOSOME positioning; and
  - heterochromatization

  which result in selective gene expression or repression

http://www.ncbi.nlm.nih.gov/mesh/?term=epigenetics

Lecture Content

1. Other Titles
2. Statistical Heterogeneity
3. EBM

4. PM

5. EBM vs. PM: Conflicting Approaches
6. Solutions
7. Conclusions

Lecture Content

1. Other Titles

1. Other Titles

1.1. First Other Title

1.2. Second Other Title

1.3. Third Other Title

1.1. First Other Title

1.1. First Other Title

Battle between EBM vs. PM

1.2. Second Other Title

1.2. Second Other Titles

Is EBM coming from Mars and PM from Venus?

1.2. Is EBM coming from Mars & PM from Venus?

Yes.

EBM was developed in the context of medical education.

PM was developed in the context of clinical pharmacology.

1.3. Third Other Title

1.3. Other Titles

Is medicine a science or an art? (the larger war)

1.3. One Battle in the Science vs. Art War

EMB vs PM

is one of many battles of this war.

1.3. Other Battles in the Science vs. Art War

Empirical Observation vs.
Mechanistic Disease Models

Probabilistic and Empirical Thinking vs.
Deterministic and Explanatory Thinking

Evaluation of Interventions vs.
Discovery and Explanation

Public Health vs.
Individual Patient Health

2. Statistical Heterogeneity

2. Statistical Heterogeneity

2.1. Obvious Example with a Drug
2.2. Numerical Examples
2.3. EBM and PM

2.1. Statistical Heterogeneity: Obvious Example

2.1. Statistical Heterogeneity: Obvious Example

- We are studying the TCA effect on heart rate.

  We include in the study:
  - 5 babies,
  - 29 adults,
  - 15 dogs, and
  - 20 horses.

2.1. Statistical Heterogeneity: Obvious Example

Is there any problem?

2.1. Statistical heterogeneity: Obvious Example

- Yes, the heart rates of
  - babies
  - adults
  - dogs
  - horses

  are different.

2.1. Statistical heterogeneity: Obvious Example

Can we calculate the TCA **mean** effects on the heart rate in this sample?

2.1. Statistical Heterogeneity: Obvious Example

- No, it makes no sense.
- This is a statistically heterogeneous sample.

2.2. Statistical Heterogeneity: Numerical Examples

2.2. Numerical Examples

2.2.1. Statistical Heterogeneity: Numerical Example 1

2.2.2. Statistical Heterogeneity: Numerical Example 2

2.2.1. Statistical Heterogeneity: Numerical Example 1

2.2.1. Statistical Heterogeneity: Numerical Example 1

- Drug efficacy in active treatment during a RCT was measured with a scale:
  - 0: no response or worsening
  - 1: minimal response
  - 2: mild response
  - 3: moderate response
  - 4: excellent response

2.2.1. Statistical Heterogeneity: Numerical Example 1

- Results in 100 patients:

0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (19%)

1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 (20%)

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 (22%)

3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 (20%)

4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 (19%)

- Sample description:

m±SD: 2.0±1.4

P_{25}, P_{50}, P_{75}: 1.0, 2.0, 3.0

No heterogeneity

2.2.2. Statistical Heterogeneity: Numerical Example 2

2.2.2. Statistical Heterogeneity: Numerical Example 2

- Results in 100 patients:

0 0 (2%)

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 (96%)

4 4 (2%)

- Sample description:

m±SD: 2.0±0.4. Same mean.

P_{25}, P_{50}, P_{75}: 2.0, 2.0, 2.0

Yes, heterogeneous. Four outliers (those with 0 or 4).

2.3. Statistical Heterogeneity: EBM and PM

2.3. Statistical Heterogeneity: EBM vs. PM

	EBM	PM
Homogeneity	Assumed	Absent
Heterogeneity	Ignored	Assumed
Mean	Represents sample well	Does not represent sample
Outliers	Ignored	Crucial

3. EBM

3. EBM

3.1. History

3.2. Critiques

3.3. Relationship with Statistical Heterogeneity

3.1. History of EBM

3.1. History of EBM

3.1.1. Different Views of Definition
3.1.2. General Agreement
3.1.3. Success
3.1.4. Foundation
3.1.5. Developmental Context
3.1.6. Definitions

3.1.1. Different Views of EBM

2.1. Statistical Heterogeneity: Obvious Example

What is EBM?

3.1.1. History of EBM: Different Views

- It depends on whom you ask:
  - EBM developers proposed that EBM originated with the first use of statistics in medicine: Louis used numbers in Paris during the 1830s against bloodletting in pulmonary infections.

    http://www.ncbi.nlm.nih.gov/pubmed/8555924
  - Gerber et al.: the use of statistics is not important; rather, EBM's fundamental innovation is that it relies on and enhances a more equal relationship between physicians rather than relying on experts.

    http://www.ncbi.nlm.nih.gov/pubmed/15780507

3.1.2. General Agreement on EBM

3.1.2. History of EBM: General Agreement

- EBM was mainly developed in the 1980s at McMaster University in Canada by:
  - Guyatt (internist),
  - Sackett (epidemiologist), and
  - others.
- EBM's dissemination:
  Sackett moved to Oxford University.
- EBM became a mainstream concept in medicine after the publication of two articles:
  - *JAMA* in 1992 http://www.ncbi.nlm.nih.gov/pubmed/1404801
  - *British Medical Journal* in 1996

http://www.ncbi.nlm.nih.gov/pubmed/8555924

3.1.3. Success of EBM

3.1.3. EBM history: Success

- According to Vandenbroucke, some journals:
  - have greatly championed EBM:
    - *British Medical Journal*
    - *Annals of Internal Medicine*
    - *JAMA*
  - have kept some distance:
    - *The Lancet*
    - *New England Journal of Medicine*

http://www.ncbi.nlm.nih.gov/pubmed/9872263

3.1.4. Foundations of EBM

3.1.4. History of EBM: Foundations

- In a 2004 update of EBM's progress,
  http://www.ncbi.nlm.nih.gov/pubmed/15514320
  Guyatt et al. gave credit for the foundations of EBM to:
  - Cochrane (Scottish epidemiologist):
    clinical disciplines should summarize evidence for their practices
  - Sackett: teaching innovations
  - Feinstein: defining the principles of quantitative clinical reasoning
- However, Feinstein (*BioSocieties* 2007;2:101-4):
  - was critical of EBM until his death
  - helped to develop a patient-centered approach

Feinstein was a physician with mathematical training and is considered the founder of clinical epidemiology.

3.1.5. Developmental Context of EBM

3.1.5. History of EBM: Developmental Context

- Sackett & Rosenberg http://www.ncbi.nlm.nih.gov/pubmed/8544145

  EBM was needed due to the:
  - rapid growth of RCT
  - slow pace of updating textbooks
  - physicians' lack of time for keeping up with journals
  - lack of efficacy of CME in improving clinical competence
- Woolf: the main factor contributing to EBM's introduction was:
  - the wild variation in medical practice
  - with service overuse: ↑ costs (and sometimes underuse)

3.1.6. Definitions of EBM

3.1.6. History of EBM: Standard Definition

- Sackett et al. http://www.ncbi.nlm.nih.gov/pubmed/8555924
  - defined EBM as:
    - the conscientious,
    - explicit, and
    - judicious use of current best evidence in making decisions about individual patient care.
  - further explained:

    EBM practice means integrating
    - individual clinical expertise with
    - the best available external clinical evidence from systematic research.

3.1.6. History of EBM: Definition

- Most would agree that
  - the heart of EBM is the reliance on RCTs as the best alternative for guiding medical knowledge.

3.1.6. History of EBM: Comprehensive Definition

- Reilly very wisely acknowledged that EBM is 3 different things:
  1) a scientific hypothesis

  2) an ever-evolving body of evidence

  3) an idealized way of practicing medicine

http://www.ncbi.nlm.nih.gov/pubmed/15514321

3.2. Critiques of EBM

3.2. Critiques of EBM

3.2.1. Lack of Interest in Innovation
3.2.2. Inversion of the Role of Experience in Medicine
3.2.3. Limitations of the Scientific Approach in Medicine
3.2.4. Lack of Evidence

3.2.1. Lack of Interest in Innovation

3.2.1. Lack of Interest in Innovation

As a matter of fact, the hierarchy of EBM is just the opposite of the hierarchy for Innovation.

3.2.1.1. Hierarchy of EBM
3.2.1.2. Hierarchy for Innovation

3.2.1.1. Hierarchy of EBM

3.2.1.1. Hierarchy of EBM

1. RCTs
2. Prospective follow-up studies
3. Retrospective follow-up studies
4. Case-control studies
5. Anecdotal: case report and series

http://www.ncbi.nlm.nih.gov/pubmed/18336067

3.2.1.2. Hierarchy for Innovation

3.2.1.2. Hierarchy for Innovation

- Vandenbroucke explains that the hierarchy for innovation is inverted:
  1. Anecdotal: case reports and series, findings in data, literature
  2. Case-control studies
  3. Retrospective follow-up studies
  4. Prospective follow-up studies
  5. RCTs

http://www.ncbi.nlm.nih.gov/pubmed/18336067

- EBM does not focus on innovation.

3.2.2. Inversion of the Role of Experience in Medicine

3.2.2. Inversion of the Role of Experience in Medicine

- Dr. de Leon's view:
  EBM is a double-edged sword, it is:
  - an inversion of the role of experience and, at the same time,
  - a culmination of the introduction of the scientific method in medicine.

3.2.2. Inversion of the Role of Experience in Medicine

- EBM is a definitive departure from the prior 2,500 years, which was based on mentorship with a more experienced physician, ideally an “expert”.
- In this traditional approach to learning medicine:
  - The medical student rotated with a mentor who taught the student the art of medicine.
  - Then the physician practiced by himself and acquired experience by making mistakes (sometimes lethal for patients).
  - A few became physician mentors.

3.2.2. Inversion of the Role of Experience in Medicine

- Traditional approach:
  - the older the physician,
  - the more wise and
  - experienced he or she was supposed to be.

- The EBM approach has inverted this process: older physicians tend to be less experienced with EBM updates. http://www.ncbi.nlm.nih.gov/pubmed/15710959

3.2.3. Limitations of the Scientific Approach in Medicine

3.2.3. Limitations of the Scientific Approach in Medicine

- EBM is the culmination of the introduction of the scientific method in medicine.
  - In the last 500 years: ↑ scientific knowledge in physician mentoring
  - In the 20th century: RCT development and its ↑ adoption by government drug agencies
  - More importantly, RCTs are combined in meta-analyses by using an average.
- The realization that RCTs and meta-analyses should be the cornerstone for medical decisions/education led to EBM.

3.2.3. Limitations of the Scientific Approach in Medicine

3.2.3.1. Limitations of Meta-Analysis

3.2.3.2. Limitations of RCTs

3.2.3.1. Limitations of Meta-Analysis

3.2.3.1. Limitations of Meta-Analysis

- Feinstein's Critique:
  - "Faith" in EBM is expanded mainly by experts.
  - Physicians usually defer to epidemiologists or other experts, since they rarely master the "secretive" art of summarizing average drug responses using meta-analytic techniques.

http://www.ncbi.nlm.nih.gov/pubmed/9428837

3.2.3.2. Limitations of RCTs

3.2.3.2. Limitations of RCTs

- RCTs used to □ test drug efficacy and
  □ gain FDA approval for marketing

  usually deal:
  - with short-term drug response
  - in otherwise healthy
  - and uncomplicated patients
  - who are also willing to enter RCTs.
- Physicians, however,
  - □ often deal with chronically ill patients
  - □ who usually take multiple medications
  - □ and can be uncooperative with meds.
- Physicians are interested in drug response
  - □ after many months or years of treatment
  - □ in all types of patients.

3.2.3.2. Limitations of RCTs

- Practical or pragmatic trials:
  - increase the representativeness of RCTs.
  - focus on effectiveness (vs. efficacy).

- There are very few or no pragmatic clinical trials for most medical problems.

3.2.4. Lack of Evidence

3.2.4. “Lack of Evidence” Critique

- Knotterus & Dinant wisely stated that:
  - Medicine-based evidence should be a prerequisite for EBM.
  - Future research methods must find ways of accommodating clinical reality, not ignoring it. http://www.ncbi.nlm.nih.gov/pubmed/9374881

- The more difficult the patient, the less evidence is available for treatment.

3.3. EBM's Relationship with Statistical Heterogeneity

3.3. EBM's Relationship with Statistical Heterogeneity

3.3.1. The Relevance of Statistical Heterogeneity
3.3.2. Senn's Critique of RCTs
3.3.3. The Surprising Conclusion about RCTs

3.3.1. The Relevance of Statistical Heterogeneity for EBM

3.3.1. The Relevance of Statistical Heterogeneity

- In 1997 Feinstein and Horwitz emphasized the problem of lack of homogeneity in RCTs.

http://www.ncbi.nlm.nih.gov/pubmed/9428837

- Statisticians only started focusing on this issue very recently:

“The average patient may not represent all patients.”

3.3.1. The Relevance of Statistical Heterogeneity

Again repeat to yourself:

“The average patient may not represent all patients.”

3.3.1. The Relevance of Statistical Heterogeneity

- Two solutions for dealing with patient heterogeneity:
  - *a priori*: using stratification
  - *a posteriori*: using subgroup statistical analyses to test for heterogeneity in treatment effects. http://www.ncbi.nlm.nih.gov/pubmed/20704705

3.3.2. Senn's Critique of RCTs

(*Drug Infor J* 2001;35:1479-94)

http://dij.sagepub.com/content/35/4/1479.full.pdf+html

(BMJ 2004;329:966-8)

http://www.ncbi.nlm.nih.gov/pubmed/15499115

3.3.2. Senn's Critique of RCTs

- Senn is a statistician with long experience in working on industry RCTs.
- He has provided a comprehensive critique on statistical heterogeneity.
- Senn criticizes EBM:
  - RCTs provide information on averages.
  - The calculation of an average number assumes that all patients benefit equally. Therefore, NNT assumes that efficacy is the same in all patients.

3.3.2. Senn's Critique of RCTs

- RCTs are designed to test average differences between treatments.
- 3 main sources of error variability are:
  - between-patient variability
    (the average differences between patients)
  - patient-by-treatment interaction
    (the extent to which differences between treatments differ from one patient to another)
  - within-patient error
    (the variability shown from treatment period to treatment period when the same patient is given the same treatment).

3.3.2. Senn's Critique of RCTs

- Again this is a very complex but key issue:

3 main sources of error variability are:

- **between-patient variability**
  (the average differences between patients)
- **patient-by-treatment interaction**
  (the extent to which differences between treatments differ from one patient to another)
- **within-patient error**
  (the variability shown from treatment period to treatment period when the same patient is given the same treatment)

3.3.2. Senn's Critique of RCTs

- Using simple words:

  3 main sources of error variability are:

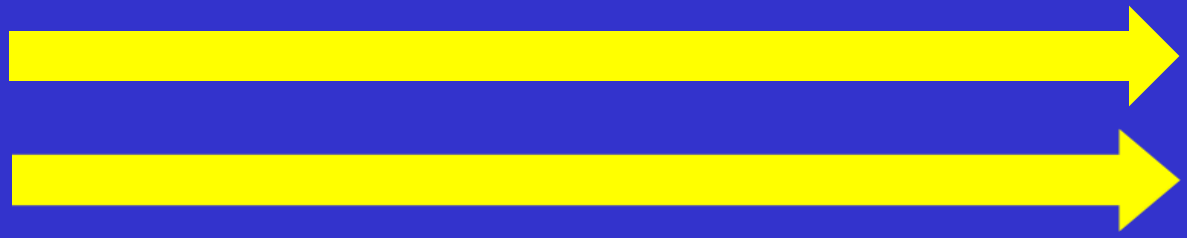
  - **Different patients are different.**
  - **Patients respond differently to treatments.**
  - **The same patient may respond differently to a treatment at different times.**

Types of RCTs

- Parallel RCTs: patients are randomized to:

  Treatment A

  Placebo



- Cross-over RCTs: patients are randomized to:

  Treatment A → Placebo

  Placebo → Treatment A

3.3.2. Senn's Critique

- Parallel RCTs cannot distinguish between the 3 types of error variability.
- Cross-over RCTs (each patient receives the treatment and control conditions) cannot distinguish between:
  - patient-by-treatment interaction and
  - within-patient error.
- Cross-over RCTs:
  - are better than parallel RCTs.
  - are not sufficient to distinguish error variability.

3.3.3. The Surprising Conclusion about RCTs

3.3.3. The Surprising Conclusion about RCTs

- RCTs can tell:
  - which treatments are effective,
  - but not which patients should receive them.

(J Clin Epidemiol 1998;51:289-95)

http://www.ncbi.nlm.nih.gov/pubmed/9539883

(*Perspect Biol Med* 2002;45:549-68)

http://www.ncbi.nlm.nih.gov/pubmed/12388887

4. PM

4. PM

4.1. History
4.2. Critiques
4.3. Relationship with Statistical Heterogeneity

4.1. History of PM

4.1. History of PM http://www.ncbi.nlm.nih.gov/pubmed/15372089

- In 1909, Garrod called it "**chemical** individuality".
- In the 1950s, severe ADRs were seen in a few patients.
- In 1959, Vogel referred to "pharmacogenetics".
- In the 1960s-70s:

  Two phenotypes were described for several drugs.
  - poor metabolizers (abbreviated as PMs in other presentations)
  - extensive metabolizers
- In the 1980-90s:
  - various CYP genes
  - alleles were associated with poor metabolism
  - TCA ultrarapid metabolizers:

    CYP2D6 gene duplication or multiplication
  - other pharmacokinetic genes

4.1. History of PM: The 1990s

- Parallel genetic testing: DNA microarrays
- The new term was “pharmacogenomics”.
- In 1997, “personalized prescription” (*Science* 278:2039):
  - was defined as tailoring drugs to genetic makeup.
  - would **“SOON”** reach clinical practice.
- In 2000, the human genome race ended (*Time* 2000; July 3:18-23).
- Predictions were that the generalized use of personalized prescription would begin in:
  - **2015** (according to *Time* 1999;Nov 8:68-9).
  - **2020** (according to *JAMA* 2001;285:540-4).

http://www.ncbi.nlm.nih.gov/pubmed/11176855

4.1. History of PM: First Decade of the 21st Century

- In 2008, Nebert et al.:
  Genetic mechanisms are very complex and knowing the DNA sequence may not be enough.
  - The function of 1/3 of the genes is unknown.
  - CNVs influence gene function.
  - Epigenesis influences gene function.

  http://www.ncbi.nlm.nih.gov/pubmed/18464043
- DNA microarrays introduced into clinical practice:
  - In 2006, the FDA approved the first one:
    The AmpliChip CYP450 Test
    http://www.ncbi.nlm.nih.gov/pubmed/16706732
- Other microarrays have been developed for:
  - proteinomics: proteins
  - transcriptomics: resulting from DNA transcription
  - metabonomics: metabolic products

4.2. Critiques of PM

4.2. Critiques of PM

4.2.1. Senn’s Critique
4.2.2. Dr. de Leon’s View

4.2.1. Senn’s Critique of PM

4.2.1. Senn's Critique of PM

- Prior slides (3.3.2) described Senn's criticisms of RCTs:
  - they provide information on averages, and
  - the calculation of an average summary number (NNT) assumes that all patients benefit equally.
- Senn
  - explains that genetic variability is **part** of patient-by-treatment interaction in RCTs, but its relevance is untested.

In summary, the relevance of pharmacogenetics on RCTs is untested.

4.2.2. Dr. de Leon's View

4.2.2. Dr. de Leon's View

(Pharmacol Res 2009;59:81-9) http://www.ncbi.nlm.nih.gov/pubmed/18996200

- Personalized prescription is a branch of PM.
- Predictors of drug response should consider pharmacology to be a mechanistic science.
- Pharmacological mechanisms are:
  - pharmacokinetic and
  - pharmacodynamic.

Both types of mechanisms are influenced by:

- genetics
- environmental factors
- personal factors

4.2.2. Dr. de Leon's View

(*Acta Neuropsychiatr* 2014 ;26:327-33) http://www.ncbi.nlm.nih.gov/pubmed/25455256

- Each drug is different:
  - different mechanisms
    - specific pharmacokinetics &
    - specific pharmacodynamics

    The differences are explained by the arbitrariness of the processes of human evolution.
  - variations in the relevance of genetic factors

4.3. PM's Relationship with Statistical Heterogeneity

4.3. PM and Statistical Heterogeneity

	EBM	PM
Homogeneity	Assumed	Absent
Heterogeneity	Ignored	Assumed
Mean	Represents sample well	Does not represent sample
Outliers	Ignored	Crucial
RCT: Stratification	Not needed	For outliers
Heterogeneity analyses	Not needed	Stratification not done

4.3. PM and Statistical Heterogeneity

- If one wants to defend EBM as being a good representation of drug response:
  - the mean represents the population well
  - a standard statistical test can be used

- If one wants to defend PM as being a better representation of drug response than EBM:
  - a good number of subjects are outliers
  - outliers are excluded from the usual analyses
  - mean results do not represent outliers
  - outliers should be studied separately

4.3. PM and Statistical Heterogeneity

We are studying one drug.

Is EBM a better approach?

or

Is EBM a better approach?

4.3. PM and Statistical Heterogeneity

We are studying one drug.

Is EBM a better approach?

or

Is EBM a better approach?

The answer depends on the frequency of outliers.

4.3. PM and Heterogeneity: Example of Frequency

- % of outliers in the population:
  - <1%: unlikely that well-designed studies using RCTs will ever be conducted in them
  - 1-10%: the main question is the financial cost and practicality of the RCTs considering the outliers.
  - 50% (e.g., one sex): “too many”. It would be a difficult task to convince a company to develop this drug for only ½ the market, when the competing drugs are approved for all.

4.3. PM and Heterogeneity: Example of Very Low Frequency

- As example of extremely low frequency of outliers, less think we want to study:
  - Poor metabolizers for CYP2D6 and CYP2C19
    - do not have CYP2D6
    - do not have CYP2C19
    - metabolizes poorly most antidepressants
    - are approximately 1/1,000 in all races

  You need to genotype up to 50,000 patients to find 50 of them to study them.

  RCTs on this very rare outliers will never be completed.

5. EBM vs. PM: Conflicting Approaches

5. EBM and PM: Conflicting Approaches

- Prior articles on the tension between EBM and PM:
  - economic issues
  - practical implementation
  - Miles et al. (*J Eval Clin Pract* 2008;14:621-49):

    http://www.ncbi.nlm.nih.gov/pubmed/19018885

    EBM has "been effectively sidelined and marginalized" by PM.
- This presentation (and editorial) focuses on
  - historical issues
  - statistical issues

  These cannot be ignored if this tension is to be understood.

5. EBM and PM: Conflicting Approaches

PM

The more that PM is needed to properly use a drug,

the more the drug response is not homogeneous and

the more an EBM approach will be detrimental.

5. EBM and PM: Conflicting Approaches

“EBM is the way to go.”

When we assume drug response is
homogeneous and
well-represented by the mean,
we simply ignore the patients
who need personalized prescription.
Are we ignoring <1%, 10% or 50%
of the sample?

5. EBM and PM: Conflicting Approaches

"EBM is the way to go."

A pharmaceutical company may feel safe in ignoring "a few" outliers.

The outlier patients and their families may not be so happy about being ignored.

5. EBM and PM: Conflicting Approaches

“EBM is the way to go.”

Balancing the public health approach vs. the individualized approach is difficult.
It is easy to see why
EBM and PM may be enemies
in times of limited economic resources and increasing health expenses due to technological developments.

6. Solutions

6. Solutions

6.1. Advances in Scientific Methodology to Bring EBM and PM Closer

6.2. Educating the Defenders of One Approach about the Virtues of the Other

6.3. Openness Toward Advances in Science, in General, that May Rescue Medicine from this Stalemate

6.1. Advances in Scientific Methodology to Bring EBM and PM Closer

6.1.1. Developments in Scientific Methodologies for PM

6.1.2. Studying Variability in Drug Response Among Individuals

6.1.3. Personalizing RCTs

6.1.4. Personalizing EBM Guidelines

6.1.1. Developments in Scientific Methodologies for PM

6.1.1. PM: Developments in Scientific Methodology

- Reviews describe designs for pharmacogenetic studies including RCTs.
  (*Clin Pharmacol Ther* 2011;89:198-209)
  http://www.ncbi.nlm.nih.gov/pubmed/21209614

- As long as no funding sources are identified for these studies, this is mostly a theoretical exercise.

- Off-patent drugs and rescuing withdrawn drugs: complex cases for finding funding.

6.1.2. Studying Variability in Drug Response Among Individuals

6.1.2. Studying Variability in Drug Response

- The literature describes 3 methods for studying the variability of drug response:
  - pharmacogenetic twin studies
  - repeated drug administration studies
  - replicate cross-over trials

6.1.2. Studying Variability in Drug Response Among Individuals

6.1.2.1. Pharmacogenetic Twin Studies

6.1.2.2. Repeated Drug Administration Studies

6.1.2.3. Repeated Period Cross-Over Trials

6.1.2.1. Pharmacogenetic Twin Studies

6.1.2.1. Pharmacogenetic Twin Studies

- Pharmacogenetic twin studies:
  They compare monozygotic vs. dizygotic twins
  (*Pharmacogenom* 2010;11:215-26) http://www.ncbi.nlm.nih.gov/pubmed/20136360
  are limited to:
  - short-term studies (single dose), and
  - pharmacokinetic studies

- Rarely do 'natural experiments' happen:
  Monozygotic twins take same drug and have discordant responses.

6.1.2.2. Repeated Drug Administration Studies

6.1.2.2. Repeated Drug Administration Studies

- Repeated drug administration studies: proposed by Kalow, a Canadian expert in pharmacogenetics
  (*Curr Pharmacogenomics Person Med* 2005;3:215-26)
  - They compare 2 variations in drug response: inter-individual vs. intra-individual
    - Inter-individual variations in drug response:
      (Senn calls this "between-patient variability".)
      An individual responds differently to a drug from the way others respond. It can be explained by genetics (but also by other factors).
    - Intra-individual variations in drug response:
      (Senn calls this "within-patient error".)
      An individual responds to the same drug differently at different times. It CANNOT be explained by genetics (but it can be explained by epigenetic factors; see definition of epigenesis).

6.1.2.2. Repeated Drug Administration Studies

- If you decide to use repeated drug administration studies to study genetic influences on drug response:
  Dr. de Leon recommends:
  - using reliable measures, and
  - eliminating known environmental factors
    - pharmacokinetics: inhibitors and inducers
    - pharmacodynamics: tolerance which may be due to epigenetic changes

6.1.2.3. Repeated Period Cross-Over Trials

6.1.2.3. Repeated Period Cross-Over Trials

- Senn: after a RCT, use "repeated period cross-over trials". This is doing an '*n*-of-1 trial' in all patients.
  - They help to separate:
    - between-patient variability
      (Kalow's inter-individual variations in drug response)
    - patient-by-treatment interaction
      (not addressed by Kalow)
    - within-patient error
      (Kalow's intra-individual variation in drug response).

6.1.3. Personalizing RCTs

6.1.3. Personalizing RCTs

- Examples of using the PM approach in RCTs:
  - stratification by gene variations
  - stratification by inducers or inhibitors

6.1.4. Personalizing EBM Guidelines

6.1.4. Personalizing EBM Guidelines

- Incorporating a more patient-centered approach (*Am Board Fam Pract* 2004;17:59-67)

  http://www.ncbi.nlm.nih.gov/pubmed/15014055

- Incorporating a mechanistic pharmacological approach (*Clin Pharmacol Ther* 2011;89:662-73)

  http://www.ncbi.nlm.nih.gov/pubmed/21412232

- Rethinking the hierarchy of grading recommendations, particularly for drug safety (*JAMA* 2008;300:2417-9)

  http://www.ncbi.nlm.nih.gov/pubmed/19033592

6.2. Educating Each Side About Their Weaknesses and the Virtues of the Other Side

6.2. Educating Each Side About Their Weaknesses and the Virtues of the Other Side

- For the PM side:
  - Completing meta-analyses is not easy.
  - Statistical training of US physicians is weak, but improving statistical training in medical school is difficult.
- For the EBM side:

  Many EBM scientists do not understand that:
  - theories and
  - mechanistic interpretations

  are crucial in medicine.
- Collaboration between both sides (EBM & PM) is needed to advance medicine.

6.3. Openness Toward Advances in Science

6.3. Openness Toward Advances in Science

6.3.1. Understanding How Science Advances
6.3.2. "Complexity" (a new way of scientific thinking)
6.3.3. Initial Steps in Using the Scientific Approach for Defining an "Expert"

6.3.1. Understanding How Science Advances

6.3.1. Understanding How Science Advances

- Science: a complex trial-and-error historical process led by experts (scientists)
- Major advances can be explained by:
  - charge (discoveries solve problems that are quite obvious but in which the way to solve the problem is not so clear)
  - challenge (discoveries are explained by a new acknowledgment of the limitations of scientific thinking)
  - chance (serendipitous findings made by "prepared minds")

(*Science* 2007;317:761-2) http://www.ncbi.nlm.nih.gov/pubmed/17690282

6.3.1. Understanding How Science Advances: Medicine

- Ioannidis (a physician) focused on the limitations of scientific thinking in medicine:
  - A majority of published findings are false (including some from RCTs).
  - "Important" articles and "important" journals are even more prone to falsehood.
  - Replication (the cornerstone of establishing a scientific finding) is discouraged.
  - Personal and financial biases contribute to the dissemination of false findings.

  (*PLos Med* 2008;5:e201) http://www.ncbi.nlm.nih.gov/pubmed/18844432

6.3.1. Understanding How Science Advances: Medicine

- Dr. de Leon thinks that PM and EBM approaches may not be so different in that:
  - both are full of false findings.
  - both are biased, but their varying traditions result in different biases.

- Naylor stated that clinical medicine consists of:
  - a few things we know
  - a few things we think we know (but probably don't)
  - lots of things we don't know at all

  (*Lancet* 1995;345:840-2) http://www.ncbi.nlm.nih.gov/pubmed/7898234

6.3.2. Complexity

6.3.2. Complexity

- A new concept in scientific thinking is called “complexity”.
- The concept reflects the complexity of scientific exploration and the need for complex computer models.
- Their names when introduced in medicine:
  - Theory: “network medicine”
  - Computer models: “network analyses” (*Nat Rev Genet* 2011;12:56-68)

http://www.ncbi.nlm.nih.gov/pubmed/21164525

6.3.2. Complexity

- Dr. de Leon thinks that it seems hard to convince currently practicing physicians that, in the future, specific treatment decisions will be made by:
  - ignoring their "subjective" experience and
  - introducing 100s/1000s of pieces of data
    - from genetic or
    - other biomarkers

    into a computer model that will "magically" provide the answer.

6.3.3. The Scientific Approach to Defining Experts

6.3.3. The Scientific Approach to Defining Experts

- The scientific approach is not particularly successful in:
  - studying and
  - explaining

  the more complex concepts of human life, but researchers from educational sciences are trying to define what an “expert” is.

6.3.3. The Scientific Approach to Defining Experts

- Who are the experts in medicine?
  It is a very complex question.
  It can be explored in 3 ways:
  - Who are the experts in medical education?
  - Who are the experts in medical practice?
  - Who are the experts in medical research?

6.3.3. Defining Who are Experts in Medicine

6.3.2.1. Who are the Experts in Medical Education?
6.3.2.2. Who are the Experts in Medical Practice?
6.3.2.3. Who are the Experts in Medical Research?
6.3.2.4. Conclusion

6.3.3.1. Who are the Experts in Medical Education?

6.3.3.1. Who are the Experts in Medical Education?

- Experts in medical education:
  - are mainly decided at the local level.
    "Experts" are those who are more frequently chosen as "mentors", from which to learn medicine, by the young physicians:
    - medical students, and
    - residents.
  - Textbooks are becoming less and less influential.

6.3.3.2. Who are the Experts in Medical Practice?

6.3.3.2. Who are the Experts in Medical Practice?

- Experts in medical practice:
  - are mainly decided at the local level by physicians:
    - from other specialities: referring patients
    - from the same speciality:

      <u>The best definition of an expert:</u>

      those physicians who are consulted on difficult cases by other physicians from the same specialty.
  - by patients when they have freedom to choose physicians:
    - marketing is very influential
    - poor choices are frequent

6.3.2.3. Who are the Experts in Medical Research?

6.3.3.3. Who are the Experts in Medical Research?

- Experts in medical research:
  - have one of only three types of medical expertise that can be accessed:
    - at the non-local level (all over the world)
    - using the scientific approach
- Articles can be compared by number of citations. The more journals you include, the more citations. They are available at:
  - Research Gate (free, but need to login) https://www.researchgate.net/home
  - Google Scholar (free) http://scholar.google.com/
  - Web of Science (not free), http://ipscience.thomsonreuters.com/product/web-of-science/

Google Scholar (free) offers the Web of Science number of citations of each article.

6.3.3.3. Who are the Experts in Medical Research?

- Researchers can be compared by:
  - Number of total citations in all their articles
    - Research Gate: articles are selected by the author
      not well-established
      includes many journals
    - Web of Science: you need to select articles for each author
      well-established
      includes less journals
  - "h" index: Hirsch proposed summarizing the impact of the researcher's articles with 1 number.

(*PNAS 102:16569-72, 2005*) http://www.ncbi.nlm.nih.gov/pubmed/16275915

(*PNAS 104:19193-8, 2007*) http://www.ncbi.nlm.nih.gov/pubmed/18040045

6.3.3.3. Who are the Experts in Medical Research?

- "h" index examples with round numbers:
  - "h" index =10 (at least 10 articles with ≥10 citations)
    This requires at least 100 (10 x 10=100) total citations.
    The researcher probably has hundreds of citations.
  - "h" index =33 (at least 33 articles with ≥33 citations)
    This requires at least 1,089 (33 x 33=1,089) total citations.
    The researcher probably has thousands of citations.
  - "h" index =100 (at least 100 articles with ≥100 citations)
    This requires at least 10,000 (100 x 100=10,000) total citations.
    This high number is rare among psychiatric researchers.

6.3.3.4. Experts in Medicine: Conclusion

6.3.3.4. Experts in Medicine: Conclusion

- Experts in medical research:
  - Article citations reflect the current opinion of researchers all over the world.
  - It is likely that the most innovative and historically important experts may need time to be recognized.
  - It is dominated by non-medical experts (PhDs).
- Local experts in medical education/practice:
  - are crucial for local trainees and local physicians.
  - according to Polanyi, the process of learning medicine with a mentor requires some implicit learning:
    - it is difficult to translate into words and
    - is learned by example.

(*Yale J Biol Med* 1990;63:47-61) http://www.ncbi.nlm.nih.gov/pubmed/2356625

7. Conclusions

7. Conclusions

- An armistice between EBM and PM
  - is possible,
  - but will require changing how the various interested parties think about the complex pharmacological mechanisms of drug responses.
- New RCT methodological designs are needed:
  - stratification using mechanistic hypotheses
  - Senn's "repeated period cross-over trials" after RCTswhen possible
- Already-marketed drugs lack information on personalization unless funding for new studies with following designs:
  - pharmacogenetic twin studies
  - repeated drug administration designs

  (inter-individual vs. intra-individual variation)

7. Conclusions

- "Personalized EBM" is a new term (*Ann Intern Med* 2009;151:JC6-2,JC6-3) http://www.ncbi.nlm.nih.gov/pubmed/20008752
- It can only be based on
  - □ prescribers gaining a better understanding of pharmacological mechanisms, and
  - □ general acknowledgment by all parties:
    - government agencies,
    - health organizations,
    - health providers and
    - patients

  of the limitations of both EBM and PM.
- EBM and PM □ are complementary
  - □ yet antagonistic in their approaches.

Collaboration between experts in both fields is needed.

Thank you

for surviving so many statistics and so much thinking.

Answers

1. A
2. A
3. A
4. B
5. A
6. D
7. B
8. A
9. A
10. A