Basic Science in
Evidence Based
Medicine

Adam La Caze

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Based Medicine
Basic Science and
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Mechanisms and
randomised trials
The Hierarchy of Data
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Summary

Basic Science in Evidence Based Medicine

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September 2009

Outline

Evidence Based Medicine (EBM)

A new paradigm for medical practice is emerging. Evidence-based medicine de-emphasises intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research.

Evidence-Based Medicine Working Group (1992). *JAMA*, 268(17):2420–2425.

EBM's Hierarchy of Evidence

Phillips et. al. (2001) Oxford Centre for Evidence-Based Medicine

Level	Therapy/Prevention, Aetiology/Harm
1a	Systematic review of RCTs
1b	Individual RCT
1c	All or none
2a	Systematic review of cohort studies
2b	Individual cohort study
2c	'Outcomes' research; Ecological studies
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

EBM and Basic Science

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The hierarchy implies a clear course of action for physicians addressing patient problems: they should look for the highest available evidence from the hierarchy.

Guyatt and Rennie 2002, Users Guide to the Medical Literature

If a study wasn't randomised, we suggest that you stop reading it and go on to the next article in your search.

Straus et al. 2005, Evidence-Based Medicine: How to practice and teach.

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A sound understanding of pathophysiology is necessary to interpret and apply the results of clinical research. . . . Understanding the underlying pathophysiology allows the clinician to better judge whether the results are applicable to the patient at hand . . .

The Evidence-Based Medicine Working Group, 1992 JAMA

Aims

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1. Provide a basic framework for integrating the mechanisms of basic science with the analysis and interpretation of randomised clinical trials

2. Show that the mechanisms of basic science play an important role in specifying, analysing and interpreting evidence from randomised trials. (Internal validity)

3. Show that the mechanisms of basic science play an important role in *applying* the results of randomised trials to patients. (External validity)

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Basic Science and Mechanisms

- ▶ The basic medical sciences (physiology, pharmacology, immunology ...) are a rich source of how-actually models, which are at least pragmatically complete in the context of the basic sciences.

- ▶ It is important to distinguish between the how-actually models provided by the basic sciences and the clinical *application* of these models. The how-actually models of basic science can be used to develop phenomenological and/or how-possibly models to assist answering clinical questions

- ▶ These 'clinical' models are very important for medical decision making.

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The Hierarchy of Data Models

- ▶ Patrick Suppes 1962 'Models of Data' provides a useful account of the relation between the mechanisms proposed by basic science and data from randomised trials.

- ▶ The hierarchy of models emphasises the importance of intermediary theories between direct observation and general theory. The general theory is provided by the how-actually model.

- ▶ Suppes' account is germane for a couple of reasons:

  - ▶ It fits nicely within a philosophy of experiment. (Suppes account is central to Mayo's (1996) philosophy of experiment).
  - ▶ It captures the arguments that are made in analysing and interpreting data from clinical research.
  - ▶ It is independent of a preferred account of statistical inference.

The Hierarchy of Data Models

- A 'model of a theory' is 'a possible realisation of the theory in which all the valid sentences are satisfied'. (Suppes 1962)
- 'Models of experiment' and 'models of data' are defined similarly.
- The theories of basic science (in the context of clinical medicine) make claims about how the pharmacological characteristics of drugs will interact with the physiological characteristics of patients.
- The general theory (mechanism) is at a level of abstraction. In order to test the clinical application of the theory, models of the theory, models of experiment and models of data are required.

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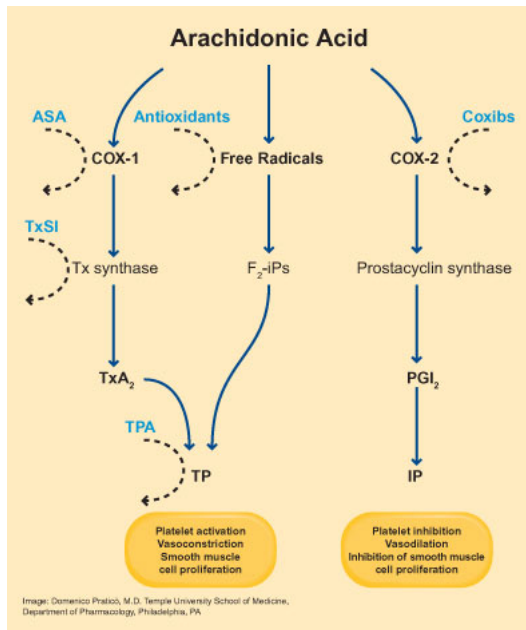Based Medicine
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Rofecoxib and Thrombotic Risk

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Image: Domenico Praticò, M.D. Temple University School of Medicine, Department of Pharmacology, Philadelphia, PA

Rofecoxib and Thrombotic Risk

General Theory Does selective inhibition of COX-2 increase the risk of thrombotic events?

Model of theory If the theory is true: $RR_\mu = \mu_R/\mu_C > 1$, where $RR\mu$ is the population relative risk.

Experiment APPROVe: a trial randomising patients to treatment with rofecoxib or placebo.

Model of experiment A number of claims are part of the model of the experiment, each can be independently tested. For example a central assumption is that the random allocation has resulted in comparable groups of patients.

Data A range of raw data is collected.

Model of data Represents the raw data in a way the general theory can be tested. For example, $RR_X = X_R/X_C > 1$, where RR_X is the relative risk observed in the sample.

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Assessing External Validity

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Summary

- ▶ Clinical trials provide data on the effects of an intervention in a *sample* of patients under *experimental conditions*. Clinicians need to assess:
    - Does the sample of patients within the trial reflect the target population (the population who will receive the intervention)?
    - The results of the trial reflect the average response to the intervention. Do patients with different characteristics respond differently?
- ▶ How-actually models of the basic sciences and clinical how-possibly models are vital for assessing external validity.
- ▶ If EBM's hierarchy of evidence is taken on face value the challenge of external validity becomes intractable.

The Challenge of External Validity

What is required is a degree of humility in the face of an issue for which there is not statistical or clinical solution. . . . Randomised trials have not, however, answered the question of which individuals actually benefit from medical interventions. This, surely, is the key issue in clinical research for the next millennium.

Smith and Egger, 1999 J Clin Epi.

Rofecoxib and External Validity

- ▶ There are many differences between the patients involved in APPROVe and the primary target population for treatment with rofecoxib. Indeed the target population were *excluded* from APPROVe.

- ▶ Basic science (and the mechanisms provided by basic science) provide an account of how the sample of patients in APPROVe is relevant to the target population.

- ▶ Basic science (and the mechanisms provided by basic science) also provide an account of how the results of APPROVe are (or are not) relevant to individual patients.

Summary

▶ EBM tells clinicians to base therapeutic decisions on the results of randomised trials *rather than* basic science.

▶ If this claim is taken seriously (and it appears some proponents of EBM do take this claim seriously) then it renders the challenge of assessing external validity impenetrable.

▶ Basic science is needed for therapeutic decisions. Indeed therapeutic decisions are best informed by basic science (and the mechanisms of basic science) rigourously tested and refined by clinical research.