

SPPS 255: Principles of Pharmacoepidemiology

Monday, 31 March 2025

PROPOSED PLAN

Course Schedule (subject to change)

Week 1 – Introduction to Pharmacoepidemiology / Pharmacoepidemiology study designs

Week 2 – Discussion on readings

Week 3 – Administrative databases (e.g., claims, registries, electronic health records)

Week 4 – Discussion on readings

Week 5 – Bias and Confounding / Methods to address bias and confounding (e.g., propensity score matching)

Week 6 – Discussion on readings

Week 7 – Medication Use Evaluation / Drug Use Evaluation/Drug Use Review

Week 8 – Discussion on readings

Week 9 – Pharmacovigilance / FDA and safety

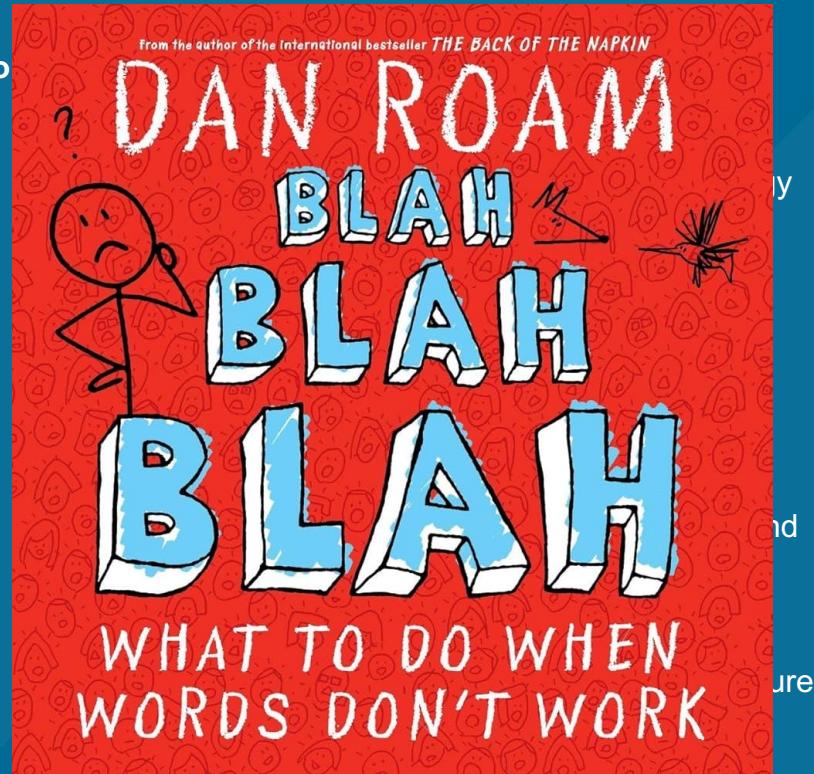
Week 10 – Bioethical issues and Closing Statement

THIS QUARTER...

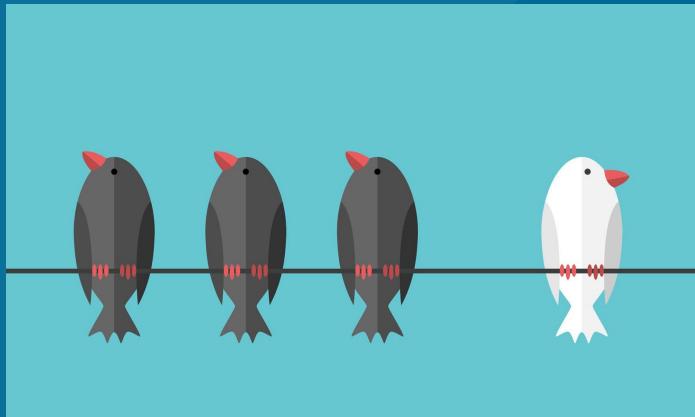
Course Objectives

1. Describe the basic principles of pharmacoepidemiology
2. Understand the application of pharmacoepidemiology in the context of healthcare practice
3. Understand the role of pharmacovigilance in healthcare practice and policy
4. Critically evaluate the research methods used in pharmacoepidemiology research
5. Identify and develop strategies to address bias, confounding, and effect modification
6. Understand the purpose and distinguish between a Drug Use Evaluation, Medication Use Evaluation, and Drug Use Review
7. Describe the impact of pharmacoepidemiology on practice and policy.
8. Critically evaluate the pharmacoepidemiology literature

THIS QUARTER...



Independent thinker



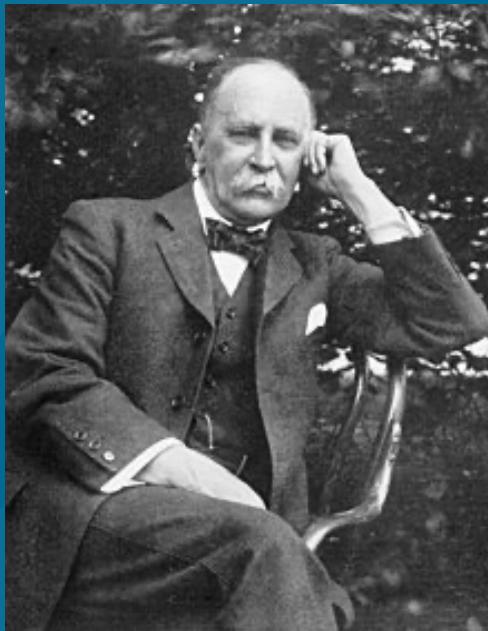
WHAT THIS ELECTIVE IS ABOUT

We'll talk about pharmacoepidemiology, but...



Come prepared with one question about pharmacoepidemiology

WE NEED EVIDENCE



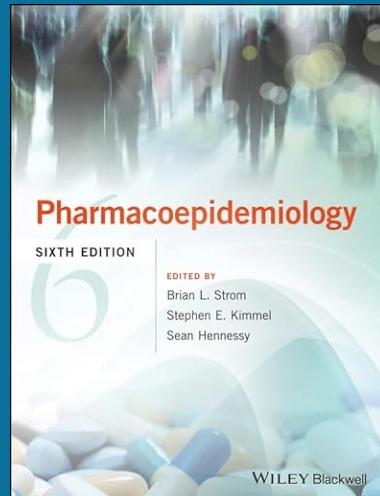
*“The practice of medicine is
an art, based on science.”*

- *William Osler*

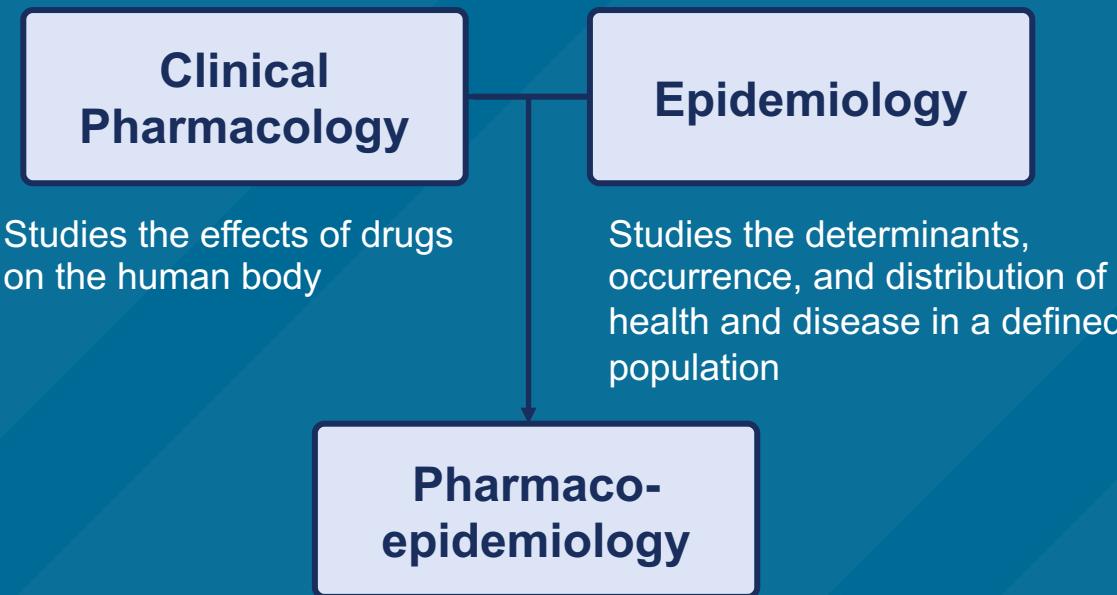
DEFINITION

“Pharmacoepidemiology is the study of the use of and the effects of drugs in large number of people.”

- Brian L. Strom



PHARMACOLOGY + EPIDEMIOLOGY



EXAMPLES

ORIGINAL CONTRIBUTION

JAMA-EXPRESS

Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

PREVENTIVE MEDICINE 20, 47–63 (1991)

Estrogen Replacement Therapy and Coronary Heart Disease: A Quantitative Assessment of the Epidemiologic Evidence^{1,2}

MEIR J. STAMPFER, M.D.,*†,‡ AND GRAHAM A. COLDITZ, M.D.*‡

*The Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts; †Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; and ‡Technology Assessment Group, Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators*

Lancet 2004; 364: 221–29
Published online
November 5, 2004
<http://image.thelancet.com/extras/04art10237web.pdf>
See Comment page 1995
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Summary The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint.

Findings We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20742 patients) the relative risk from randomised controlled trials was 2.30 (95% CI 1.22–4.33, $p=0.010$), and 1 year later (64 events, 21 432 patients) it was 2.24 (1.24–4.02, $p=0.007$). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; $p=0.41$) or trial duration ($p=0.82$). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0.86 (95% CI 0.75–0.99)) and could not have explained the findings of the VIGOR trial.

Interpretation Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

PHARMAEOPIDEIOLOGY GOALS

Risk-benefit assessment

Adverse drug effects and Safety

Post-marketing studies

Comparative Effectiveness Research

PHARMAEOEPIDEMIOLOGY GOALS



LET'S TALK ABOUT HUMANS...



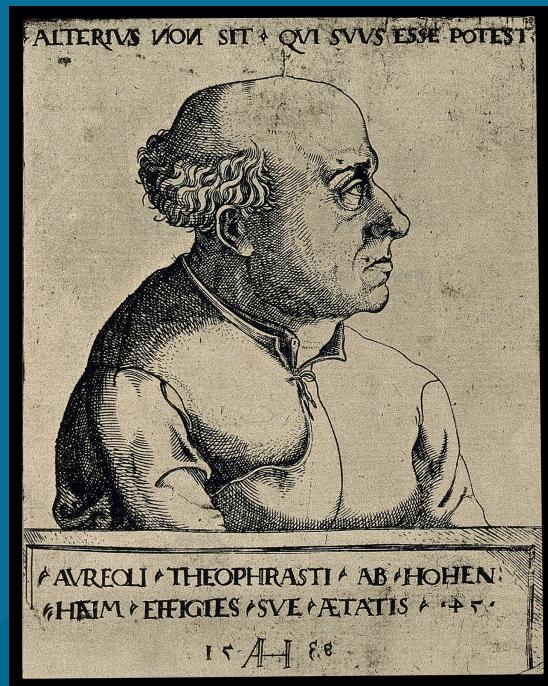
DECISIONS HAVE CONSEQUENCES



MEDICATIONS ARE POISONS

“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.”

- Paracelsus



THALIDOMIDE CASE

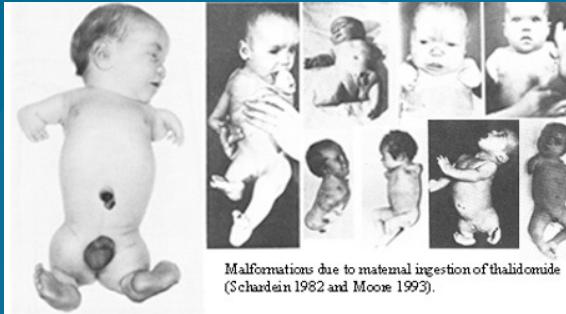
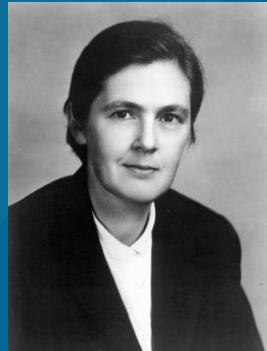
“Deficiencies in all areas were found during the initial review of the thalidomide application and in several subsequent resubmissions.” – Kelsey (1988)

Thalidomide was used in the 1950s and 1960s for pregnancy-induced nausea/vomiting in Europe

Pressure to approve its use in US markets, but Dr. Frances Kelsey delayed approval to gather more evidence on its safety profile

>10,000 children developed phocomelia

Changed how toxicology was performed for new drugs entering the market



Malformations due to maternal ingestion of thalidomide
(Schadein 1982 and Moore 1993).



1. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease [published correction appears in Toxicol Sci. 2012 Feb;125(2):613]. Toxicol Sci. 2011;122(1):1-6. doi:10.1093/toxsci/kfr088
2. Vargesson N, Stephens T. Thalidomide: history, withdrawal, renaissance, and safety concerns. Expert Opin Drug Saf. 2021;20(12):1455-1457. doi:10.1080/14740338.2021.1991307
3. Kelsey FO. Thalidomide update: regulatory aspects. Teratology. 1988;38(3):221-226. doi:10.1002/tera.1420380305

COSTS ASSOCIATED WITH DRUG ADVERSE EVENTS

Between 2014 and 2018, a total of 5113 outpatient onset adverse drug reactions (ADRs) were reported to the VA Adverse Drug Event Reporting System (VADERS)^[1]

Of which 2792 (~55%) ADRs resulted in hospitalization

Enoxaparin-hemorrhage (drug-ADR) pairing was associated with \$29,535

Hydrochlorothiazide/lisinopril-angioedema pairing was associated with \$6951

1. Aspinall SL, Vu M, Moore V, Jiang R, Au A, Bounthavong M, Glassman PA. Estimated Costs of Severe Adverse Drug Reactions Resulting in Hospitalization in the Veterans Health Administration. JAMA Netw Open. 2022 Feb 1;5(2):e2147909. doi: 10.1001/jamanetworkopen.2021.47909. PMID: 35142836; PMCID: PMC8832171.

DRUG-RELATED MORBIDITY AND MORTALITY

Sub-optimal therapy (e.g., non-adherence) is associated with negative externalities

Estimated annual cost of sub-optimal therapies was \$528.4 billion (2016US\$)^[1]

Approximately 16% of total US health-related expenditures in 2016

Individuals who experience treatment failure were associated with \$2481; new medical problem, \$2610; and both, \$2572, annually

1. Watanabe JH, McInnis T, Hirsch JD. Cost of Prescription Drug-Related Morbidity and Mortality. *Ann Pharmacother*. 2018;52(9):829-837. doi:10.1177/1060028018765159

MEDICATION ERRORS (RELATED TO PHARMACOEPIDEMIOLOGY)

“To err is human: building a safe health system”^[1]

Focus is on the system, not the person

The New York Times

Ex-Nurse Convicted in Fatal Medication Error Gets Probation

RaDonda Vaught, a former nurse at Vanderbilt University Medical Center in Tennessee, said at her sentencing, “I’m sorry’ doesn’t seem like enough.”

HEALTH & WELLNESS

Should a nurse’s medical error be considered a crime?

Nurses’ groups are calling the case of RaDonda Vaught a ‘dangerous precedent.’ Prosecutors say it’s the right verdict after a woman died as a result of ‘gross neglect.’

SPECIAL ARTICLE

Changes in Practice among Physicians with Malpractice Claims

Authors: David M. Studdert, LL.B., Sc.D., Matthew J. Spittal, Ph.D., Yifan Zhang, Ph.D., Derek S. Wilkinson, Ph.D., Harnam Singh, Ph.D., and Michelle M. Mello, J.D., Ph.D. [Author Info & Affiliations](#)

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TheUpshot
THE NEW HEALTH CARE

A Missed Opportunity for the Malpractice System to Improve Health Care

A small percentage of doctors keeps doing a large share of the damage.

Share full article 235

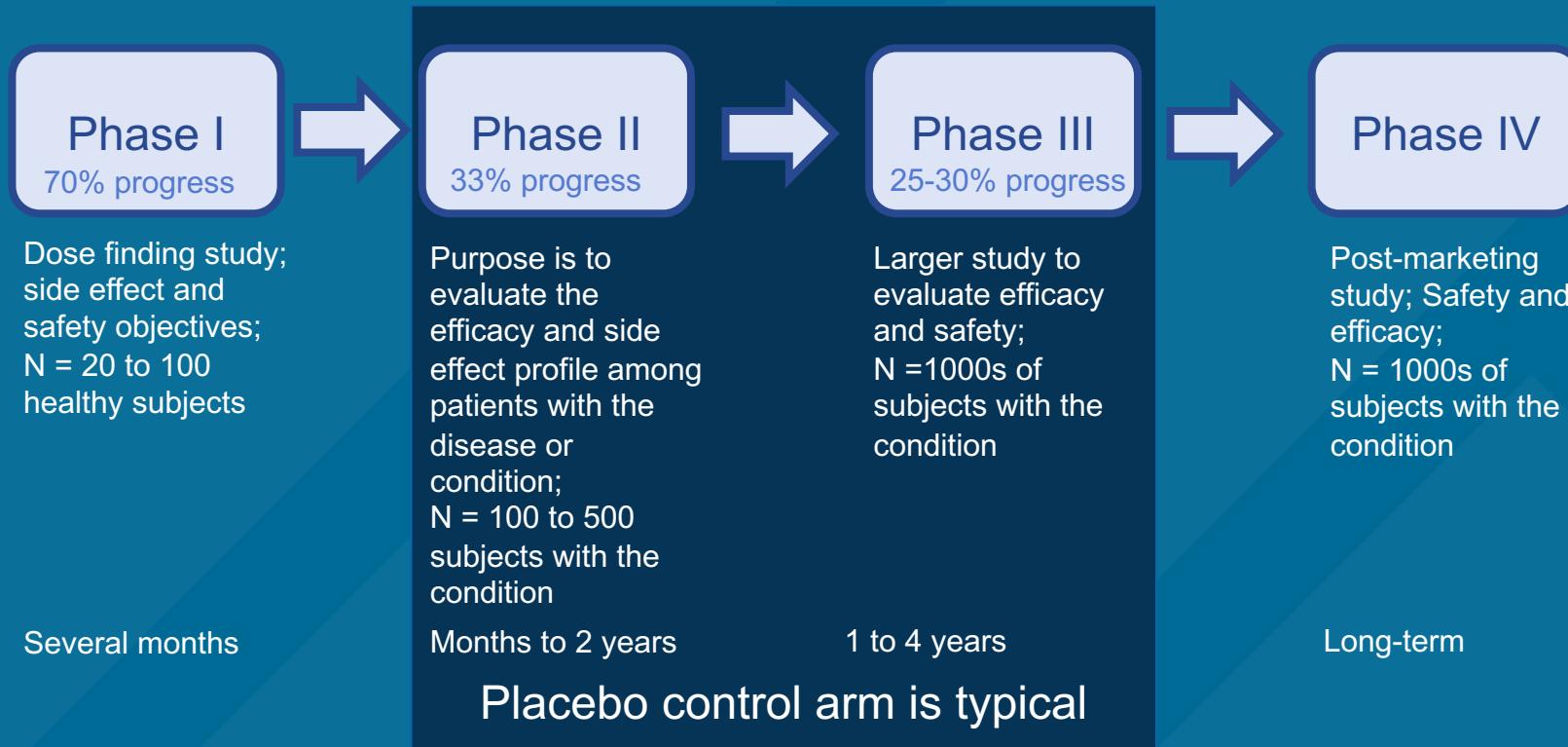
By Aaron E. Carroll

May 27, 2019

Approximately, 2% of doctors accounted for about 39 percent of all claims in the US.^[4]

1. Institute of Medicine (US) Committee on Quality of Health Care in America, Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is Human: Building a Safer Health System*. Washington (DC): National Academies Press (US); 2000.
2. Medina E. “Ex-Nurse Convicted in Fatal Medication Error Gets Probation.” New York Times. 15 May 2022. ([link](#))
3. Palowski A. “Should a nurse’s medical error be considered a crime? TODAY. 13 May 2022. ([link](#))
4. Carroll. “A Missed Opportunity for the Malpractice System to Improve Health Care. New York Time. 27 May 2019. ([link](#))

PHASE I, II, III, AND IV TRIALS



COMMON STUDY DESIGNS

Features	RCT	Cohort	Case-control	Cross-sectional
Study population	Highly selected population; highly controlled environment	Diverse population observed in a range of settings	Diverse population observed in a range of settings	Diverse population observed in a range of settings
Directionality	Exposure is assigned before outcome is ascertained	Exposure is assigned before outcome is ascertained	Outcome is ascertained before exposure	Exposure and outcome are ascertained simultaneously
Primary use	Causal interpretation; efficacy	Rare exposure	Rare outcome	Hypothesis generation
Analysis	Simple statistical tests	Multivariable methods to account for confounding	Multivariable methods to account for confounding	Multivariable methods to account for confounding
Internal validity	+++	+	+	+
External validity	++	+++	+++	+++

Source

CAUSAL INFERENCE

Statistical association is a state where researchers can infer relationships between variables through statistical testing (e.g., treatment A is associated with an increase in side effects)

Causal inference is the state where researchers can infer relationships between variables under conditions that are changing (e.g., changes that are induced by a treatment or intervention); it cannot be inferred from statistical associations alone, but from premises that invoke concepts of causation

CAUSAL INFERENCE (HILL'S CRITERIA FOR CAUSATION)

Criteria	Description
Strength	Strong associations > Weak associations
Consistency	Repeated observations of associations in different populations and scenarios
Specificity	Cause leads to a single effect (not multiple effects) ¹
Temporality	Cause must precede the effect in time ²
Biologic gradient	Dose-response relationship
Plausibility	Biological plausibility or mechanism that is logical (or theoretical)
Coherence	Does not contradict with what we know about the nature and history of the disease
Experiment	Hypothesis testing
Analogy	Similar observations in other scenarios

1. This is not considered valid (Hill also had reservations).
2. This is a necessary component of causation

IS THIS THE BEST MODEL FOR CAUSATION?

“None of my nine viewpoints can bring indisputable evidence for or against the cause and effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”

- Austin Bradford Hill



COMPARATIVE EFFECTIVENESS RESEARCH

“A rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy.”

Evidence synthesis

- Systematic review
- Meta-analysis

Evidence generation

- Pragmatic studies

Dissemination

- Identify priority topics
- Knowledge translation (e.g., guidelines)
- Knowledge exchange / utilization (e.g., decision-support system)
- Assessment / Implementation process

GUIDELINES FOR GOOD PHARMACOEPIDEMIOLOGY PRACTICES (GPP)

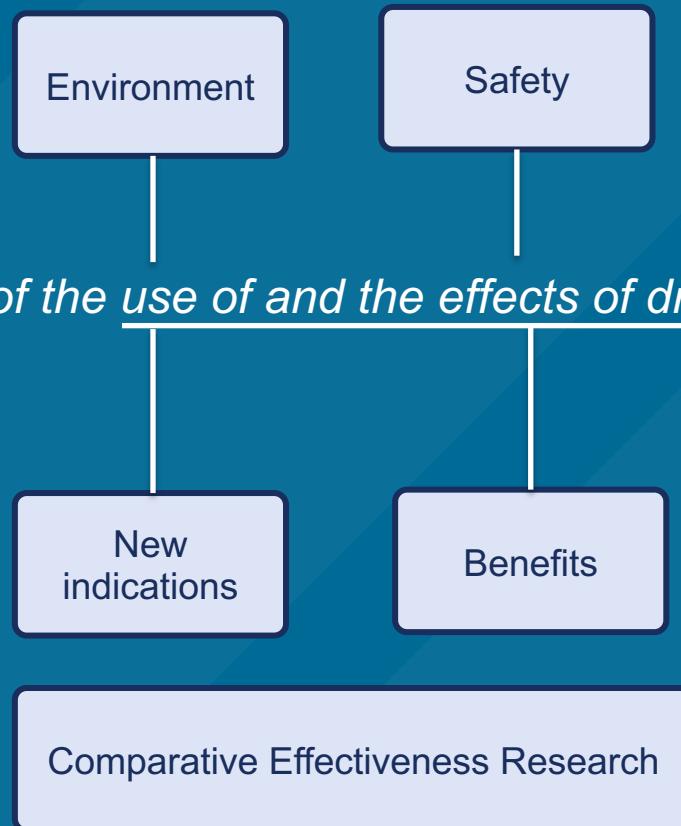
GPP Goals ([link](#))

- To assist researchers in adhering to good pharmacoepidemiologic research principles, including the use of pharmacoepidemiologic studies for risk management activities and CER.
- To promote sound pharmacoepidemiologic research by encouraging rigorous data collection, analysis, and reporting.
- To provide a framework for conducting and evaluating pharmacoepidemiologic studies.
- To facilitate the appropriate utilization of technical resources by promoting careful study design and planning of study conduct.
- To facilitate transparency and ethical integrity in research conduct

BACK TO THE DEFINITION...

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- Brian L. Strom



PROPOSED FRAMEWORK

Biomedical Ethics

Pharmacoepidemiology aims

Environment

Safety

New
indications

Benefits

Comparative Effectiveness
Research

Pharmacoepidemiology approach

Design

Analysis

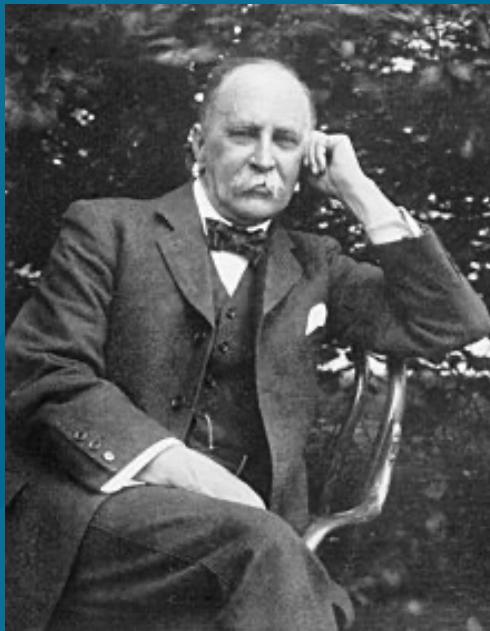
Data
infrastructure

Data
collection

MUE

Pharmaco-
vigilance

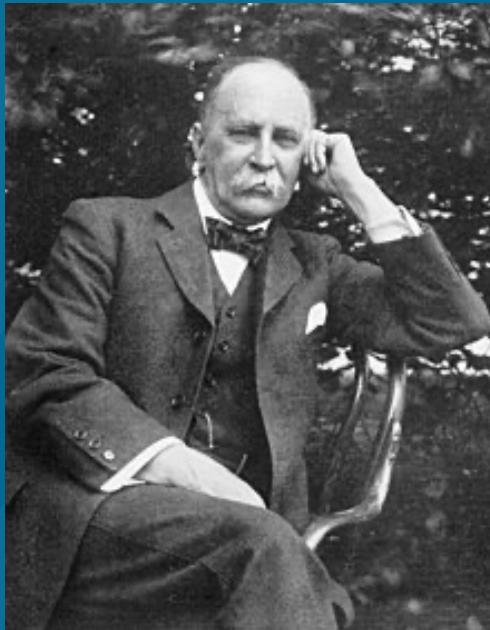
LET'S RETURN TO OSLER...



*“The practice of medicine is
an art, based on science.”*

- William Osler

ALL OF US ARE BIASED



“Every primitive tribe retains some vile animal habit not yet eliminated in the upward march of the race.”

- *William Osler (AKA E Y Davis)*

LASTLY,...

"To reach an optimal decision in any given clinical situation, evidence must be applied to an individual patient who has her or his own values, preferences, life situations, and goals. Treating not only the disease but also the patient as a whole requires both understanding and application of the best evidence, as well as the skills and behaviors physicians bring to their own practice of the art of medicine."

- Soko Setoguchi and Ian Chi Kei Wong

ADDITIONAL RESOURCES

[GitHub Site](#)



PLACE HOLDER

Place holder

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy