Pharmacoepidemiology

Maribel Salas MD, MSc, DSc

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Outline

- Definition
- Relationship with other disciplines
- Research questions answered by PE
- Phases of drug development
- Postmarketing surveillance
- Historical background
- Study design

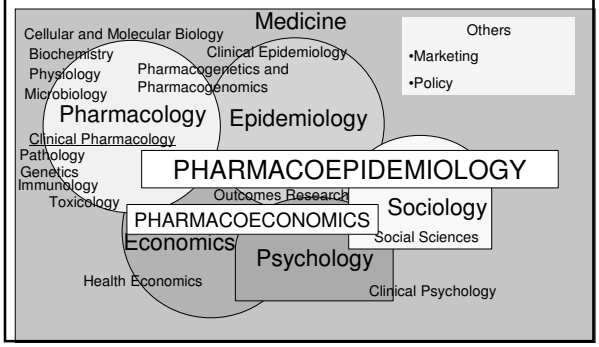
What is Pharmacoepidemiology?

Pharmacoepidemiology. Definition

- Discipline that study the frequency and distribution of health and disease as a result of the use and effects (beneficial and adverse) of drugs in human populations.
- Aims:
  - Describe
  - Explain
  - Control
  - Predict

Uses and effects of drugs in a defined time, space and population

Pharmacoepidemiology and Other Disciplines



What are the differences between Clinical Pharmacology and Pharmaco-epidemiology?

What Research Questions Are Answered by PE?

- What is the effect of “X” drug on “Y” outcome?
- What are the most common uses/adverse events of “X” drugs?
- How
- Why
- Where
- When

do “X” drugs are used in “Z” population?

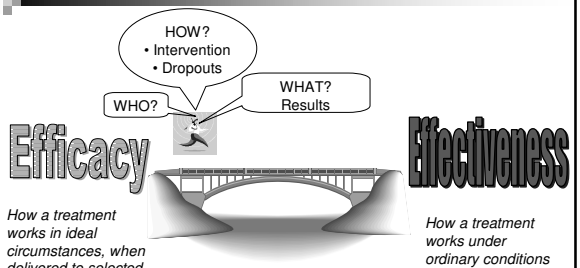
Phases of Drug Development

	PHASE I	
STUDIES IN VITRO AND IN VIVO	Who? Healthy volunteers, small number	
	Why? Safety, biological effects, pharmacokinetics profile, dosage range, duration of action and drug interactions	
	By Whom? Clinical Pharmacologists	
ANIMAL TESTING	**PHASE II**	**PHASE IV**
•SHORT TERM	Who? Selected patients (up to 300 patients)	Who? Patients given drug for therapy
•LONG TERM	Why? Therapeutic efficacy, dose range, kinetics, metabolism	Why? Adverse reactions-labeling changes, patterns of drug utilization, additional indications discovered, pricing negotiations, marketing
	By Whom? Clinical pharmacologists, clinical investigators	By Whom? Pharmacoepidemiologists and all physicians
Questions answered in this phase	**PHASE III**	
•Is the substance biologically active?	Who? Large sample of selected patients (500-3000 patients)	Areas:
•Is it safe?	Why? Safety and efficacy	Pharmacovigilance
	By Whom? Clinical pharmacologists, clinical investigators and pharmacoepidemiologists	Pharmacoeconomics
1-5 years (μ=2.6 yr)	2-10 years (μ=5.6 yr)	Variable
Preclinical	***Clinical***	***Postmarketing Surveillance***

Kaitlin KI, et al. J Clin Pharmacol 1987;27:542-548; Young FE, et al. JAMA1988; 259:2267-2270

Why Is Postmarketing Surveillance Needed?

- Frequently RCT use placebo as comparators to establish the efficacy of a drug.
- Efficacy, toxicity and cost of new drugs usually are not compared with alternative agents.
- Effectiveness data are limited, if any.

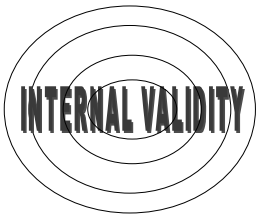


How a treatment works in ideal circumstances, when delivered to selected patients by providers most skilled at providing it.

How a treatment works under ordinary conditions by the average practitioner for the typical patient.

Efficacy: RCT

- Rigorous inclusion and exclusion criteria:
  - Limited to certain study population
  - Limited to a spectrum of a disease
  - Limited to certain number of comorbid conditions
  - Limited to certain number of medications



Effectiveness

- Heterogeneous group of patients:
  - Age
  - Gender
  - SES
- Co-morbid conditions
- Multiple treatments (pharmacologic and non pharmacologic treatments)
- Variation of patient adherence to treatment
- Variation of medical practice and compliance to guidelines
- Variation of medical knowledge among patients
- Access to care (HCS), type of care
- Costs

EXTERNAL VALIDITY

Sample Size to Detect ADR

	Statistical Power			
Frequency	95%	90%	80%	63%
1/100	300	231	161	100
1/500	1,500	1,152	805	500
1/1,000	3,000	2,303	1,610	1,000
1/5,000	15,000	11,513	8,048	5,000
1/10,000	30,000	23,026	16,095	10,000
1/50,000	150,000	115,130	80,472	50,000

Hartzema, et al. Pharmacoepidemiology, 1998

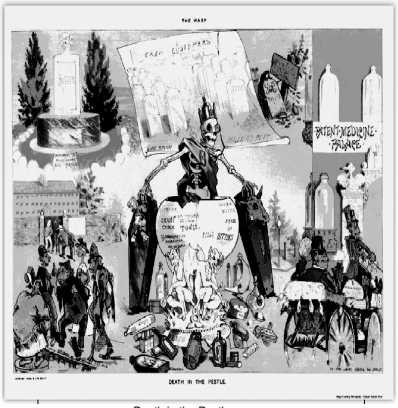
Why Is Postmarketing Surveillance Needed?

- Clinicians often use drugs in ways that are not studied in pre-marketing trials (off-label indications):
  - For different populations
  - Use different treatment regimens
  - Different indications for therapy

Why Is Postmarketing Surveillance Needed?

- Increased role of pharmacotherapy
- More rapid uptake of drug use post lunch
- Healthcare systems in general manage RISK poorly:
  - Interactions/co-prescribing
  - Failure to monitor
  - Inappropriate use

HISTORICAL BACKGROUND



Death in the Pestle

Drug Development in the USA

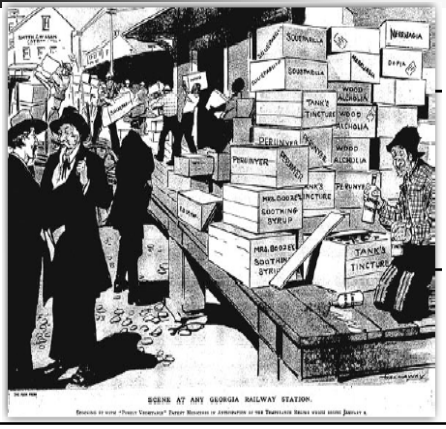
- 1906: First Act- The Federal and Food Drug Act- Interstate transport of adulterated or misbranded foods and drugs. Federal Government has the power to remove any adulterated or misbranded product from the market.
  - *In both, the "Collier's Magazine" and "The Jungle" the meatpacking industry was pilloried*

Katz R. NeuroRx 2004;1:307-316.

Burton J. Howard, chief of the Bureau of Chemistry's microchemical laboratory, is shown in the right foreground in this photo from the 1920s. Howard developed a quantitative method to detect mold in ketchup that proved to be indispensable in establishing food adulteration in court.

Drug Development in the USA

- 1937: 107 children died from renal failure as a result of elixir of sulfanilamide dissolved in diethylene glycol (Massengill Company).
  - FDA: 239 agents
  - Telegraph
  - Word of mouth



Drug Development in the USA

- 1938: Amendment to the first act secondary to those deaths. Toxicity studies were required and approval of a new drug application (NDA).

Drug Development in the USA

- 1950: Chloramphenicol associated with aplastic anemia.

  "A patient developed aplastic anemia 3 months after exposure to intravenous chloramphenicol. She died of this disease 4 years later."

  [Claudon DB, Holbrook AA. Fatal aplastic anemia associated with chloramphenicol (chloromycetin) therapy. J Am Med Assoc. 1952 Jul 5;149(10):912-4]
- 1952: AMA Council on Pharmacy and Chemistry established the first official registry of adverse drug effects-drug induced blood dyscrasias.

Katz R. NeuroRx 2004;1:307-316.

Thalidomide was invented in 1954 at the Grünenthal Labs in Germany by the inventors Dr. W. Kunz (chemical synthesis) and Dr. H. Keller (pharmacological description of sedative properties).

Drug Development in the USA

- 1960: FDA started collecting ADR reports and sponsored new hospital-based drug monitoring programs. Beginning of Pharmacoepidemiology.
- 1962: Harris-Kefauver Amendments to the Federal Food, Drug and Cosmetic Act after the phocomelia epidemic worldwide.
  - It mandated that a drug product must be safe and effective before it may be approved for marketing.
  - Preclinical studies were required in animals
  - Submission of investigational new drug (IND) was requested by FDA before any clinical study.
  - Efficacy, safety and data to support claims were required.

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Initiatives

- 1990: The American Society for Clinical Pharmacology and Therapeutics issued a position paper on the use of portmarketing drug surveillance studies for promotional purposes.
- 1992: The Prescription Drug User Fee Act allowed the US FDA to charge manufacturers a fee for reviewing New Drug Applications.
- 1996: The International Society of Pharmacoepidemiology (ISPE) issued guidelines for good epidemiology practices for drug, device, and vaccine research in the US.

FDA. Labeling and prescription drug advertising. Federal Register, 1994: 64240; JAMA, 2003;290:905-911

Initiatives

- 1997: The Food and Drug Administration Modernization Act (FDAMA) was approved.
  - It encourages studies of certain therapies being used in PEDIATRICS by providing an exclusivity incentive provision (6 months of marketing exclusivity).
  - FDA was mandated to develop, prioritize, and publish a list of approved drugs used off label and for which information on how to use them in pediatric population was needed.
    - "Betamethasone (Diprolene, Diprosone, Lotrisone). Topical betamethasone containing dermatologic products-suppression of the hypopituitary-adrenal axis in 28% to 75% of the pediatric patients depending on age and product used".

FDA. Labeling and prescription drug advertising. Federal Register, 1994: 64240; JAMA, 2003;290:905-911

Initiatives

- 2003: Medicare Prescription Drug, Improvement and Modernization Act where drugs need to show the value for money in the US.
- 2007: Vioxx. Report from the Institute of Medicine

What Can the FDA Control?

- Marketing Status
  - Approval decision
  - Withdrawal from the market
- Labeling
  - Availability of patient information
  - Trade names and packaging
- Application of Risk Management Strategies
- Restricted Access to certain facilities and/or specialists

FDA: Are Drugs Safe?

- No drug is 100% safe
- FDA definition: Benefits outweigh foreseeable risk for:
  - Specific indications
  - Specific populations
- Therefore, FDA should:
  - MAXIMIZE BENEFIT AND MINIMIZE RISK

Questions?