Introduction

Pharmacoepidemiology is the study of the use and effects of drugs in large numbers of people.

It is a growing discipline that applies epidemiological techniques to study drug use in a large population.

Just as the term implies, pharmacoepidemiology combines clinical pharmacology with epidemiology.

Pharmacology is the study of the effects of medications in humans. It pertains to using pharmacokinetics and pharmacodynamics of a patient to predict the drug effect on a patient.

Epidemiology is the study of the factors that determine the occurrence and distribution of diseases in populations.

Epidemiologists study how much disease is in a given area, who gets it, and what specific factors put individuals at risk.

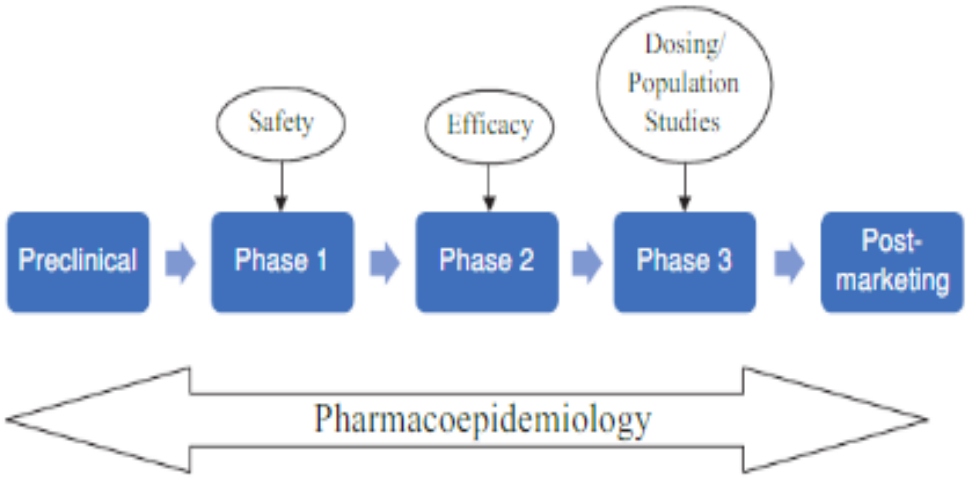
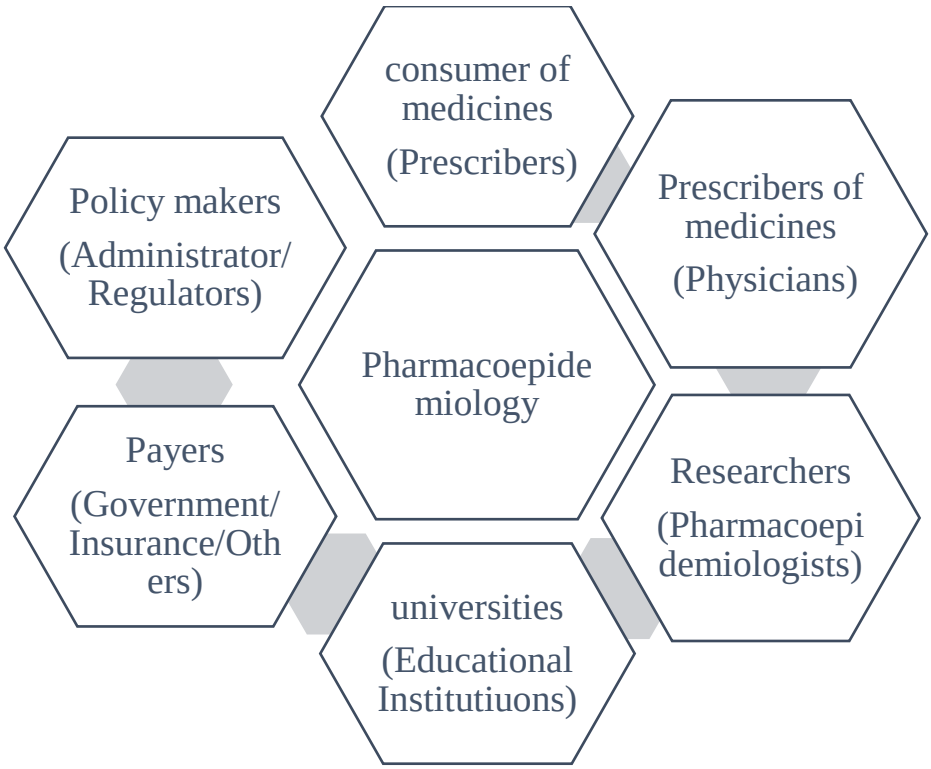


Fig: Pharmacoepidemiology through drug development and post-marketing



Aims of Pharmacoepidemiology:

The pharmacoepidemiologic studies concentrates on the period after the drug enters in the market known as post marketing surveillance (PMS)

These studies are concerned with two main aspects:

- The study of adverse effects of drugs
- The appropriate use of medicines.

Basic Concepts of Pharmacoepidemiology:

Some basic concepts of pharmacoepidemiology include:

- Cause-consequence
- Risk estimates
- Study types
- Data sources
- Methods

Potential contributions of pharmacoepidemiology:

A. Information which supplements the information available from premarketing studies-better quantification of the incidence of known adverse and beneficial effects

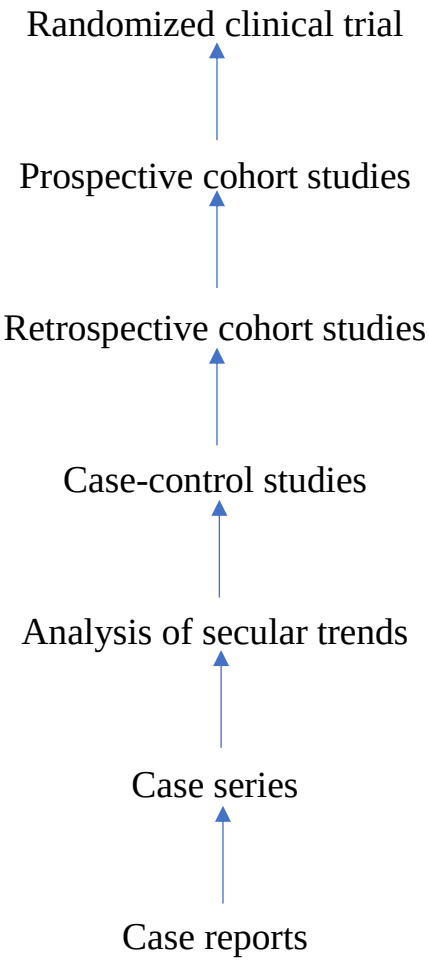
i. Higher precision
ii. In patients not studied prior to marketing
iii. As modified by other drugs and illness
iv. Relative to other drugs used for the same indication.

B. New types of information not available from pre-marketing studies
   i. Discovery of previously undetected adverse and beneficial effects
      a. Uncommon effects
      b. Delayed effects
   ii. Patterns of drug utilization
   iii. The effects of drug overdoses
   iv. The economic implications of drug use.

C. General contributions of pharmacoepidemiology
   i. Reassurance about drug safety
   ii. Fulfillment of ethical and obligations

Study designs available for pharmacoepidemiologic studies:

In hierarchical order of progressively harder to perform but more convincing



Criteria for casual nature of an association is how one can decide, how likely an association demonstrated in a particular study is, in fact, a casual association

First put forth by Sir Austin Bradford Hill in 1965

1. Coherence with existing information (biological plausibility)
2. Consistency of association
3. Time sequence
4. Specificity of association
5. Strength of association
    a) Quantitative strength
    b) Dose-response relationship
    c) Study design

In general,

- Case reports and case series- useful to suggest an association
- Analysis of secular trends and case-control studies- useful to explore these associations
- If study question warrants investment and can tolerate the delay until results become available, then cohort studies and RCTs - can be used to assess these associations more definitively.

Reasons to perform PE studies:

(A) Regulatory

(1) Required
(2) To obtain earlier approval for marketing
(3) As a response to question by regulatory agency
(4) To assist application for approval for marketing elsewhere

(B) Marketing

(1) To assist market penetration by documenting the safety of the drug
(2) To increase name recognition
(3) To assist in repositioning the drug

(a) Different outcomes, e.g., quality-of-life and economic
(b) Different types of patients, e.g., the elderly

(c) New indications
(d) Less restrictive labeling

(4) To protect the drug from accusations about adverse effects

(C) Legal

(1) In anticipation of future product liability litigation

(D) Clinical

(1) Hypothesis testing

(a) Problem hypothesized on the basis of drug structure

(b) Problem suspected on the basis of preclinical or premarketing human data

(c) Problem suspected on the basis of spontaneous reports

(d) Need to better quantitate the frequency of adverse reactions

(2) Hypothesis generating-need depends on:

(a) whether it is a new chemical entity

(b) the safety profile of the class

(c) the relative safety of the drug within its class

(d) the formulation

(e) the disease to be treated, including

- its duration
- its prevalence
- its severity
- whether alternative therapies are available

Thus, the decision to conduct a PE study can be viewed as similar to the regulatory decision about whether to approve a drug for marketing or the clinical decision about whether to prescribe a drug

In both cases, decision making involves weighing the costs and risks of a therapy against its benefits.

Sources of PE data

- Spontaneous AE reporting
- Global Drug surveillance
- Case-control surveillance

- Prescription event monitoring
  → Automated databases
  → Others

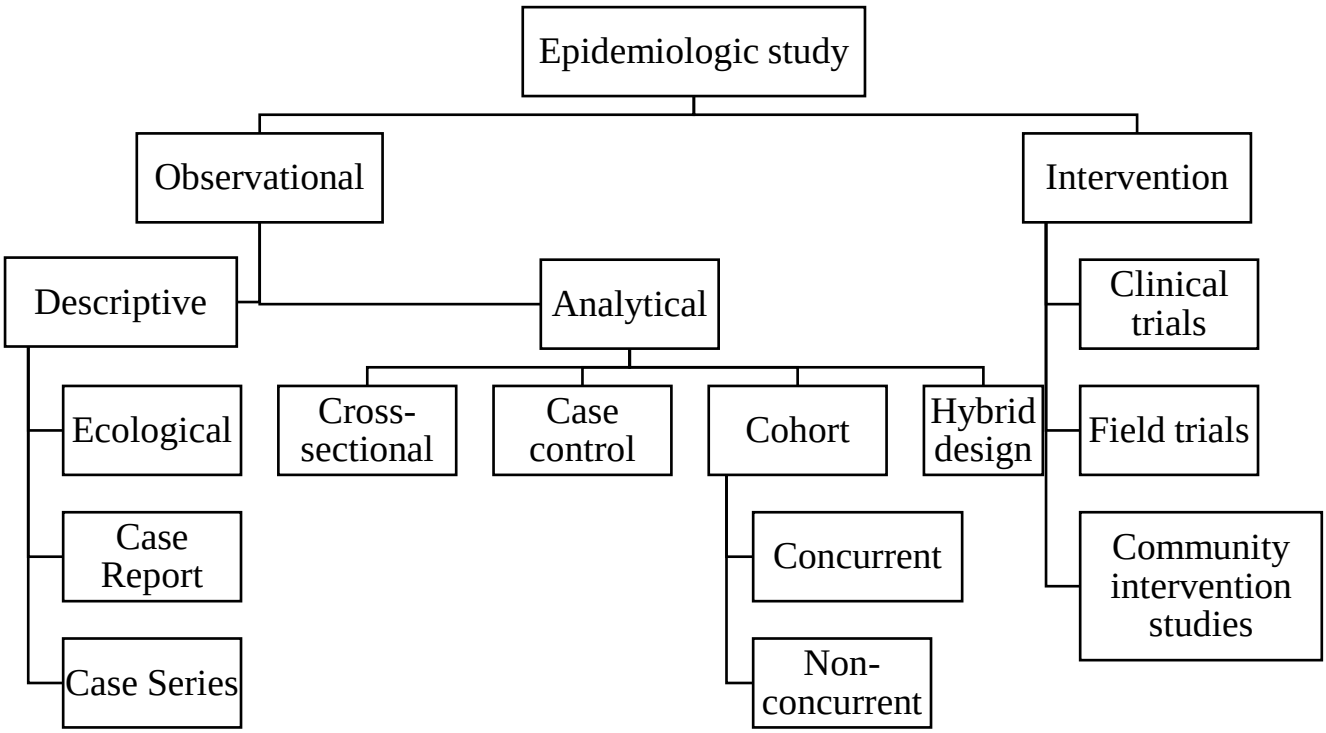
TYPES

Epidemiological studies can be divided into two main types:

1. Observational Study

2. Intervention Study

Epidemiologic Study Designs:



DESCRIPTIVE EPIDEMIOLOGY

Descriptive study: focuses on the description of the occurrence of a disease in a population.

Purpose of descriptive epidemiology:

- To generate hypothesis
- To permit evaluation of trends in health & disease and comparisons among countries and subgroups within countries.
- To provide a basis for planning, provision and evaluation of health services

- To identify problems to be studied by analytical methods and to suggest areas that may be fruitful for investigation.

CASE REPORTS

- It is the simplest form of observational study.
- During their daily routine, practitioners notice the emergence of an outcome and relate it to a drug exposure.
- The reporting of that event through an official reporting system or medical or pharmacy journal generates a signal that alerts others to the possibility of casual association.
- Eg: Zappacosta presented a case report of a patient treated with minoxidil that was discovered to stimulate the hair growth. Subsequently a topical formulation of minoxidil was developed to take advantage of that effect.

CASE SERIES

- A case series is a set of sequential case reports identified either by exposure or by outcome.
- It resembles an open trial of a drug, except that it lacks a formal protocol.
- Enlarges the information about drug use and their consequences.
- Help to confirm ADRs or new indications of the drug.
- Eg: Krishnamoorthy and king reported on the adverse effects associated with the use of olanzapine in 5 children with severe behavioural problems.
- Adverse events include: wt. gain (3/5 children), sedation (2/5 children) and akathisia (2/5 children).

Advantages

- Useful for hypothesis generation.
- Informative for very rare disease with few established risk factors.
- Usually of short duration.

Disadvantages

- Cannot study cause and effect relationships.
- Cannot assess disease frequency.

TREND ANALYSES (ECOLOGICAL STUDIES)

- It involves the plotting of data over time.

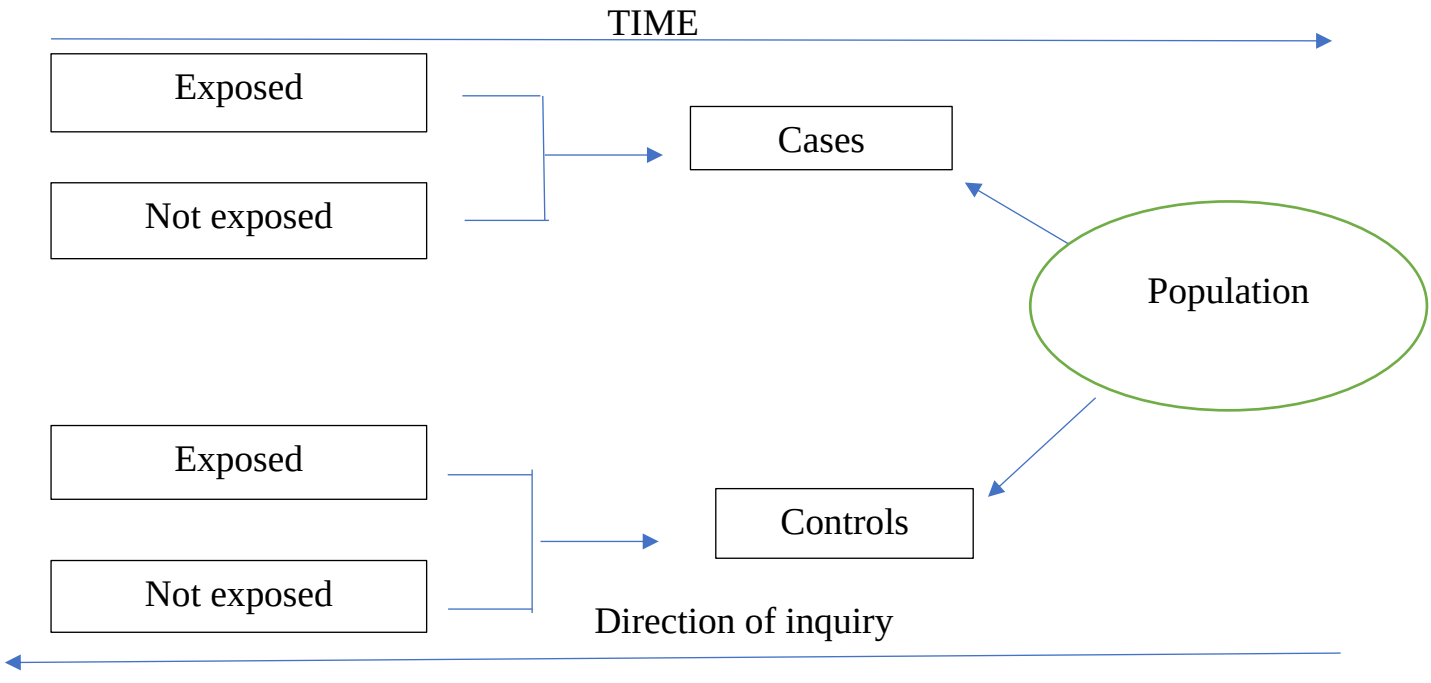
- By inspecting the plot, patterns may emerge that can explain events that have occurred.
- They are useful to provide rapid evidence for hypotheses.
- Eg: If a new pharmacy law is passed or a drug policy is implemented, we can plot drug usage over time and note what happens before and after the change. Any shift in the trend line suggest that the change in law or policy may have an impact on drug utilization.

CROSS-SECTIONAL STUDY

- These studies are examinations of the use of drugs at one specific point in time.
- They are usually done through surveys, chart reviews and data base analyses.
- They provide a view of the state of affairs at that time and an estimate of the prevalence of utilization and of outcomes.
- Such information can be used for formulary management and policy development.
- Used to compare drug use between countries or regions within in a country.
- E.g.: cross-sectional studies were published by Dua and colleagues, who examined inappropriate sale of antibiotic use in pharmacies in Nagpur.
- Such studies can identify problem areas and suggest where remedial action should be directed.

CASE-CONTROL STUDY

These studies compare cases with disease to controls without disease.



Advantages

- Useful to study multiple possible causes of a single disease.
- Useful to study uncommon diseases.
- Relatively easy to carry out.
- Rapid and inexpensive.
- Requires comparatively few subjects.
- Does not need an ethical clearance.
- There is no risk to the subject.

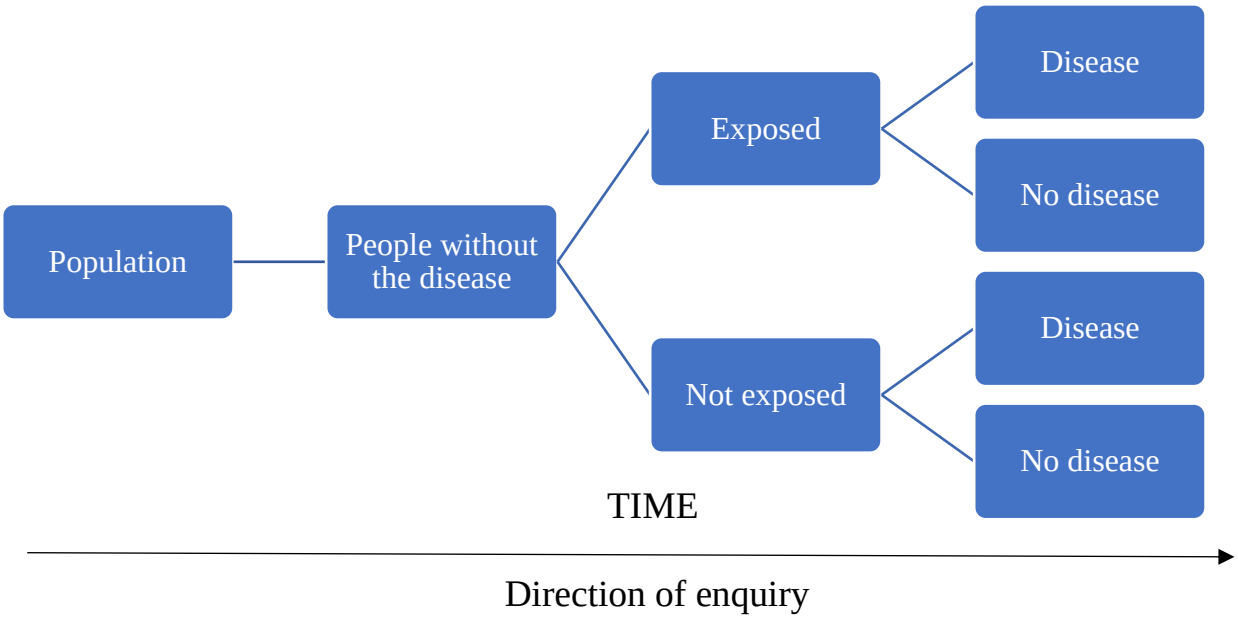
Disadvantages

- It introduces bias.
- To select an appropriate control could be difficult.
- It may be difficult to distinguish between the cause of a disease and an associated factor.

COHORT STUDY

Cohort studies identify subsets of a defined population and follow them over time, looking for differences in their outcome.

They are useful to compare exposed patients to unexposed patients.



Advantages

- There is no bias.
- It is effective for studying rare exposures.

- It allows the study of the natural history of the disease.
- It assists in determining the temporal relationship between the etiological factor & the disease.
- Can study multiple outcomes.

Disadvantages

- It takes a long time.
- It is expensive.
- Large no of subjects is needed.
- There could be changes in the standard methods or diagnostic criteria.

APPLICATIONS OF PHARMACOEPIDEMIOLOGY

- **Government agencies & Health care plans:**

Pharmacoepidemiology research is important for the government agencies like the Agency for Healthcare Research and Quality (AHRQ) and the Centres for Medicare and Medicaid Services (CMS) and Healthcare plans.

- **Practitioners:**

Pharmacoepidemiologic studies can help Pharmacists, Physicians, Nurses and other Public health care practitioners to make informed decisions about treatment for patients

- **Pharmaceutical industries:**

The pharmaceutical industry wants to understand how a drug is prescribed, used and what are all the positive and negative outcomes.

- **Academicians:**

Academicians often conduct pharmacoepidemiologic studies to find answers to practice related questions.

- **Attorneys:**

Findings from pharmacoepidemiologic studies can be used as evidence that a drug product did or didn't cause an event.

- **Consumers and Patients:**

To learn about safety and effectiveness of drug products, patients and consumers rely on pharmacoepidemiologic studies