

Concept of Risk In pharmacoepidemiology.

Definition:

It is probability of developing an outcome when exposed to a drug depending on variety of factors like age, sex, physical condition.

Measurement of risk:

Attributable risk:

It is difference in incidence rate of disease b/w exposed groups and non-exposed groups.

① It is also referred as risk difference.

② It is expressed in percent.

$$AR = \frac{\text{incidence of disease rate among exposed} - \text{incidence of disease rate among non-exposed}}{\text{incidence rate among exposed}}$$

Application:

- ① To describe clinical outcomes.
- ② It simply quantifies how much higher one rate is than that of its comparator.
- ③ It guide policymakers in planning public health interventions.
- ④ To develop approaches for disease prevention.

Advantages:

- ① Simple to calculate.
- ② Simple to understand.
- ③ maintains the information about the amount of disease.
- ④ It may be used as a priority index for ranking the importance of factors associated with the risk of disease.

Relative Risk (RR)

It is ratio of incidence of disease among exposed and incidence among non-exposed. It is also referred as risk ratio.

$$RR = \frac{\text{Incidence of disease (or death) among exposed}}{\text{Incidence of disease (or death) among non-exposed}}$$

Applications:

- ① To identify risk factors for disease
- ② To compare success rates.
- ③ It is used frequently in statistical analysis of binary outcomes.
- ④ It is suited to clinical trial data where it is used to compare the risk of developing a disease in people.

Alternatively, it is used to compare the risk of developing a side effect in people receiving a drug as compared to the people who are not receiving the treatment.

It is particularly attractive because it can be calculated by hand in the simple case. It requires large sample so that the comparison group can provide an accurate estimate of base line risk in population of interest.

Advantages:

The advantages of RR are that it is a ~~one~~ number index of the strength of association b/w disease and the proposed determinant which may be easily compared between levels of exposure to the determinant.

It is easily evaluated for statistical significance by means of chi-square ~~test~~.

The drawback that it is ~~an~~ unitless and obliterates any information about the amount of disease contained in the original incidence

Odds Ratio →

The odds ratio is the ratio of odds of an event occurring in one group to the odds of it occurring in another group.

	Outcome	No outcome
Exposed	A	B
Not exposed	C	D

$$OR = AD/BC$$

Application →

The ~~old~~ odds ratio is commonly used in survey research in epidemiology and to express the results of some clinical trials, such as in case control studies.

It provides rough estimate of relative risk and it is interpreted similarly.

rates from which it is derived. (28)

Odds Ratio:

Advantages:

1. The odds has a great advantages that it is invariable across case control, follow-up and cross-sectional studies and thus it can be used to directly compare findings of different study designs.
2. The odds ratio has an advantage that it can be computed directly from the regression coefficient of logistic regression.
3. The odds ratio is a good estimator of risk ratio if the disease is rare and the cases and controls are randomly selected from the population.

Disadvantages:

1. The odds ratio has the disadvantage that it ignores the level ratio 1:10 is the same as 10:1000.
2. OR is good for establishing causal relation but is not that useful to the public health practitioners, who is interested in knowing how much decrease in disease burden will be achieved by specific interventions.

Medication Adherence Measurement:

Definition:

Medication adherence is defined as the extent to which a patient's medication taking behaviour coincides with the intention of the advice he or she is given.

Medication adherence is one of the most important factors that determine therapeutic outcomes, especially in patient suffering from chronic illness.

There are several methods available for assessment of adherence, accurate measurement continues to be difficult at present there is no generally accepted 'Gold standard' for measuring adherence.

1. Biological assay:

Biological assays measure the concentration of a drug its metabolites or tracer compounds in the blood or urine of a patient.

These measures are intrusive and often costly to administer.

Patients who know that they will be tested may consciously take medication that they had been skipping so the tests will not detect individuals who have been non-adherent.

Drugs of food interactions, physiological differences, dosing schedules and the half-life of the drugs may influence the results.

2. Pill Count:

Counting the number of pills remaining in the patients supply and calculating the number of pills that the patient has taken since filling the prescription is the easiest method for calculating patients medication adherence.

Some data indicate that this technique may underestimate adherence in older population. Patients of non-adherence are often difficult to be determined with the simple count of pills on a certain date weeks to months after the prescription was filled.

3. Weight of Topical Medications:

Here the weight of the topical medication remaining in a tube as a measure of adherence. When compared with the patient log books of daily medication use weight estimates of adherence were considerably than patient log estimate.

4. Electronic Monitoring:

The medication event monitoring system (MEMS) manufactured by Chondex Corporation allows the assessment of the number of pills missed during a period as well as adherence to a dosing schedule.

The system electronically monitors when the pill bottle is opened and the researchers can periodically download the information to a computer.

Monitors are designed to be used by one patient with one drug.

A reader transfers the dosing history from the MEMS monitor to a MS windows based computer.

5. pharmacy Records and Prescription claims:

This method can be used primarily for medications that are taken for chronic illnesses such as hypertension.

Concerns regarding the completeness and reliability of these records have been expressed. These records provide only indirect measure of drugs consumed.

Patterns of over and under consumption for periods less than that between refills cannot be assumed.

6. patient interview:

Interviewing patients to assess their knowledge of the medication they have been prescribed and the dosing schedule provide little information as to whether the patient is adherent with the actual dosing schedule.

7. patient estimates of adherence:

Direct questioning of patients to assess adherence can be an effective method. Patients who admit to non-adherence are generally accurate in their assessment.

Cohort Study →

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

Cohort studies generally are used to compare exposed patients to unexposed patients although they can also be used to compare one exposure to another.

The term cohort is defined as the group of people who share a common characteristic or experience within the defined time period eg - Age, occupation exposure to a drug or vaccine, pregnancy, insured person.

During a weekend tournament, players from one team wore water proof SPF 35 sunscreen, while players from the other team did not wear wear any sunscreen. At the end of the valley ball tournament player skin from both teams was analyzed for texture sun damage and burns.

Comparisons of skin damage were then made based on the use of sunscreen. The analysis showed a significant difference between the cohorts in terms of the skin damage.

Indication for cohort studies:

- When there is good evidence of an association between an exposure and disease, as derived from clinical observations and supported by descriptive and case control studies.
- When exposure is rare, but the incidence of disease is high, among exposed. eg - special exposure groups like those in industries, exposure to x-ray.
- When attrition of study population can be minimized, eg - follow up is easy, cohort is stable, cooperative easily accessible.
- When ample funds are available.

Framework of a cohort study:

The basic design of a simple cohort study is shown. We begin with a group of cohort (a+b) exposed to a particular factor thought to be related to disease occurrence and a group (c+d) not exposed to that particular factor. The former is known as study cohort and the latter control cohort.

Cohort	Yes	No	total
Exposed	a	b	a+b
Not exposed	c	d	c+d

Type of cohort study:

1. Prospective cohort study.
2. Retrospective cohort study.
3. combination of retrospective and prospective cohort study.

1. Prospective Cohort Study:

A prospective cohort study or current cohort study is one in which the outcome has not yet occurred at the time the investigation begins.

Most prospective studies begin in the present and continue into the future.

2. Retrospective Cohort Study:

A retrospective cohort study or historical cohort study is one in which the outcomes have all occurred before the start of the investigation.

The investigator goes back in time, sometimes 10 to 30 years, to select his study groups from existing records and traces them forward through time from a past date fixed on the records, usually up to the present.

3. Combination of retrospective and prospective cohort study:

In this type of study, the retrospective and prospective elements are combined.

The cohort is identified from the past records and is assessed at date for the outcome, the same cohort is followed up prospectively into future assessment of outcome.

Advantages of cohort studies:

1. Incidence can be calculated.
2. Several possible outcomes related to exposure can be studied simultaneously.
3. It provides direct estimate of relative risk.

4. Dose response relation can also be calculated.

Disadvantages:

1. studies involve a large no of people.
2. It takes a long time to complete the study.
3. certain administrative problems such as loss of experienced staff, loss of finding.
4. There may be changes in the standard methods.
5. The study itself may alter people's behavior.
6. Expensive.

Non-experimental studies (observational)

1. Descriptive non-experimental studies.

A. case reports B. case series.

2. Analytical non-experimental studies.

A - case control

B - cohort study.

C - cross-sectional study.

Case Control →

By definition, a case control study involves two population case and control.

In this study, cases and controls must be comparable with respect to known confounding factor such as age, sex, occupation, social status.

Case-control studies are studies that compare cases with a disease to controls without the disease looking for differences in antecedent exposure.

A case control study was conducted to investigate if exposure to zinc oxide is a more effective skin cancer prevention

Advantage and disadvantages:

Advantage →

1. relatively easy to carry out.
2. Rapid and inexpensive.
3. Require comparatively few subjects.
4. Particularly suitable to investigate rare disease.
5. No risk to subjects.
6. Allows the study of several different etiological factors.
7. Risk factors can be identified, national prevention and control programs can be established.
8. No attrition problems because case-control studies do not require follow up of individuals in to the future.
9. Ethical problems minimal.

Disadvantages:

1. Problems of bias relies on memory or past records, ~~at~~ the accuracy of which may be uncertain, validation of information obtained is difficult or sometimes impossible.

2. Selection of an appropriate control group may be difficult.
3. We cannot measure incidence and can only estimate the relative risk.
4. Do not distinguish b/w causes and associated factors.
5. Not suited to the evaluation of therapy or prophylaxis of disease.
6. Another major concern is the representativeness of case and controls.

Aims and applications of pharmacoepidemiology:

Definition:

Pharmacoepidemiology is the study of the use and effects of drugs in larger number of people.

Aims:

To complete the evaluation of drugs made before approval, by providing reliable information concerning effectiveness, safety and utilization of medicines in realistic conditions.

- ① risk benefit assessment.
- ② Aims at providing new information not available from premarketing studies like.
- ③ Discovery of previously undetected ADR and beneficial effects.
- ④ pattern of drug utilization.
- ⑤ The effects of drug overdose.

Applications:

1. studies of drug utilization
2. Evaluating an improving physician prescribing
3. Drug utilization review
4. Special methodologic issues in pharmacoepidemiologic studies of vaccine safety.
5. pharmacoepidemiologic studies of drug safety
6. study of drug induced birth defect.
7. Risk management.
8. Medication error.
9. Hospital pharmacoepidemiology.

1. Studies of drug utilization:

It can be used to estimate drug utilization in populations by age, sex, social class and other characteristics and to identify areas of possible over or under utilization.

To monitor the utilization of specific therapeutic categories.

2. Evaluating and Improve the prescription:

Factors responsible for sub optimal prescribing

- ① Failure of clinician to keep abreast of new evidence.
- ② errors of omission.
- ③ patient demand.
- ④ Excessive promotion by pharmaceutical industry.

3. Drug utilization Review:

A DUR or DUE is an intervention in the form of an authorized structure and on going system for improve drug quality use within a given health care institution.

4. pharmacoepidemiologic studies of vaccine safety:

Vaccines are among the most cost effective and effective public health interventions have led to considerable decline in vaccine preventable disease.

A higher standard of safety is required for vaccines because of large number of persons who are exposed, some of whom are compelled to do so by law or regulation for public health reason.

5. Special Methodologic issues in pharmacoepidemiologic study of device:

1. Study hypothesis for epidemiologic studies of medical device.
2. public health impact.

6. studies of drug Induce Birth defects:

Teratogenesis is a unique adverse drug effects affecting an organism. Women of child bearing age were exclude from clinical studies because of concern about potential teratogenesis.

7. pharmacoepidemiology and risk management:

① Goal of risk management is to enhance the safe use of medicines by optimizing the balance of benefit and risk.

② This can be accomplished by increasing the benefit and/or decreasing the risk associated with the use of drug product.

8. The use of pharmacoepidemiology to study medication errors:

Medication error can occur at any stage of medication use process including prescribing, dispensing, administering and monitoring.

In most studies about a third of adverse drug events have been preventable.

9. Hospital pharmacoepidemiology:

A substantial proportion of medical care provided in a hospital, treating very ill patient with a multiple simultaneous drugs, some more toxic than drugs use in out patient.

While pharmacoepidemiology with a hospital base data recently developed ~~auto~~ automated data bases include drug administered in-hospital.

Medication errors:

Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professionals patients or consumers.

Topic-2 Measurement of outcomes in pharmacoepidemiology:

Basic Measurements in epidemiology →

Epidemiology basically focuses on measurement of mortality and morbidity in human population. The 1st requirement is therefore definition of what is to be measured and establishment of criteria or standards by which it can be measured. This is not only a prerequisite of epidemiological studies, but also one of its goals.

The clinician may not require a precise definition of disease for immediate patient care but the epidemiologist needs a definition that is acceptable and applicable to its use in large populations and that is precise and valid to enable him to identify those who have the disease from those who do not.

Clear definitions help to minimise errors in classification of data. Standardised methods of observation and recording are therefore essential before commencing any epidemiological study.

The scope of measurements in epidemiology is very broad and unlimited and includes the following:

- Measurement of mortality.

- Measurement of morbidity.

- Measurement of disability.

- Measurement of natality.

Measurement of the presence absence or distribution of the characteristic or attributes of the disease, measurement of medical needs, health care facilities, utilization of health services and other health-related events, measurement of the presence, absence or distribution of the environment.

Tools of measurement:

The epidemiologist usually expresses disease magnitude as a rate ratio or proportion. A clear understanding of the term is required for interpretation of epidemiological data. The basic tools of measurement in epidemiology are -

Rates

Ratios and

Proportions

Rate measures the occurrence of some particular event in a population during a given time period.

It is a statement of risk of developing a condition. It indicates the change in some event that takes place in a population over a period of time.

Death rate:

A rate comprises the following elements - numerator denominator time specification and multiplier. The time dimension is usually a calendar year.

The rate is expressed per 1000 on some other round figure selected according to convenience or convention to avoid fractions.

Crude rates:

These are the actual observed rates such as birth and death rates.

Specific rates - these are the actual observed rates due to specific causes or occurring in specific groups or during specific time periods.

Standardized rates - These are obtained by direct or indirect method of standardization on adjustment.

eg - age and sex standardized rates.

Ratio:

Another measure of disease frequency is a ratio. It expresses a relation in size b/w two random quantities. The numerator is not a component of the denominator. The numerator and the denominator may involve an interval of time or may be instantaneous in time.

Incidence Vs Prevalence:

1. Incidence conveys the information about the 65% of contributing the disease whereas prevalence indicates how widespread the disease is.
2. Incidence is usually more useful than prevalence in understanding the disease - etiology for eg if the incidence rate of a disease in a population increases, then there is a risk factor that promotes the incidence.

$\text{Prevalence} \approx \text{incidence} \times \text{Average duration of disease.}$

Odds Ratio $\rightarrow$

The odds ratio is the ratio of odds of an event occurring in one group to the odds of it occurring in another group.

	outcome	No outcome
Exposed	A	B
Not exposed	C	D

$$\boxed{OR = AD/BC}$$

Application $\rightarrow$

The ~~odd~~ odds ratio is commonly used in survey research in epidemiology and to express the results of some clinical trials, such as in case control studies.

It provides rough estimate of relative risk and it is interpreted similarly.

Defined daily dose (DDD):

- ① The DDD is the assumed average maintenance dose per day for a drug ~~used~~ that already have an ATC code.
- ② It should be emphasized that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose.
- ③ Doses for individual patients and patient groups will often differ from the DDD and will necessarily.

The formula for calculating DDD is as follows -

$$\text{Drug usage (DDDs)} = \frac{\text{items issued} \times \text{amount of drug per item}}{\text{Who DDD measure.}}$$

Advantages:

- ① More meaningful than simple comparisons of grams.
- ① can be applied to a large no of drugs.
- ① We can compare utilization between regions/countries and over time.

Disadvantages:

- ① DDD may present a dose that is seldom used.
- ① Not meaningful when used with paediatric drug use data.

Prescribed Daily Dose: (PDD)

The PDD will give the average daily amount of a drug that is actually prescribed.

When there is a substantial discrepancy between the PDD and the defined daily dose (DDD), it is important to take this into consideration when evaluating and interpreting drug consumption figures.

For drugs where the recommended dosage differs from one indication to another it is important that diagnosis is linked to the prescribed daily dose given.



2. Prevalence

Prevalence, sometimes referred to as prevalence rate, is the proportion of persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time. Prevalence differs from incidence in that prevalence includes all cases, both new and preexisting, in the population at the specified time, whereas incidence is limited to new cases only.

Point prevalence refers to the prevalence measured at a particular point in time. It is the proportion of persons with a particular disease or attribute on a particular date.

Period prevalence refers to prevalence measured over an interval of time. It is the proportion of persons with a particular disease or attribute at any time during the interval.

Method for calculating prevalence of disease

$$\frac{\text{All new and pre-existing cases during a given time period}}{\text{Population during the same time period}} \times 10^n$$

MONETARY UNITS

Drug use has been measured in monetary units to quantify the amounts being consumed by population

It can indicate the burden on a society from drug use

Monetary units are convenient & can be converted to a common unit, which then allows for comparison

The disadvantage is quantities of drugs actually consumed are not known & prices may vary widely



Aims:

To complete the evaluation of drugs made before approval, by providing reliable information concerning effectiveness, safety and utilization of medicines in realistic conditions.

① risk benefit assessment.

② Aims at providing new information not available from premarketing studies like.

③ Discovery of previously undetected ADR and beneficial effects.

④ pattern of drug utilization.

⑤ The effects of drug overdose.

a) Define cost utility analysis.

⇒ It is a type of cost - effectiveness analysis in which the cost per quality - adjusted life year or some other preference - based valuation of health outcome is estimated.

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TIME RISK RELATIONSHIP:

- The outcome of an exposure to a drug is related to the time.
- It is also true with risks associated with medicines.
- There is always a time related association of risk in pharmacoepidemiology.
- Certain events like anaphylactic reactions happen immediately after taking an injection while certain other risk events occur after days or months or even years.

Attributable risk:

It is difference in incidence rate of disease b/w exposed groups and non-exposed groups.

① It is also referred as risk difference.

② It is expressed in percent.

$$AR = \frac{\text{incidence of disease rate among exposed} - \text{incidence of disease rate among non-exposed}}{\text{incidence rate among exposed}}$$

Relative Risk (RR)

It is ratio of incidence of disease among exposed and incidence among non-exposed. It is also referred as risk ratio.

$$RR = \frac{\text{Incidence of disease (or death) among exposed}}{\text{Incidence of disease (or death) among non-exposed}}$$