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Definition:

- Hartzema et al (1998) have defined it as the application of epidemiologic reasoning, methods and knowledge to study the use and effects (beneficial and adverse) of drugs in human population, populations are large groups of people.
- Pharmacoepidemiology is the study of the use of and the effects of drugs in large number of people.
- The term pharmacoepidemiology obviously contain two component: Pharmaco and epidemiology

Positive outcomes:

Refer to the efficacy or effectiveness of the drug. Efficacy refers to the clinical effects of drug when used under ideal conditions.

Negative outcome:

Refers to as adverse drug events.

Pharmacoepidemiology

□Origin and Evolution:

- One of the first pharmacoepidemiologic studies occured in 1902.
- It involved the investigation into two outbreak (بروز، شيوع) of tetanus in 1901 in U.S due to contaminated vaccine.
- In St-Louis, the outbreak was due to contaminated diphtheria antitoxin, and in New Jersey due to contaminated small pox vaccine that investigation prompted the introduction of Biologics Control Act at 1902.
- A similar event in 1937 led to the requirement for manufactures to test drugs for toxicity and provide clinical safety data before drugs could be marketed.
- Thus, pharmacoepidemiology promoted protective legislation.
- Reports of serious adverse drug effects, such as aplastic anemia and the Gray baby Syndrom from chloramphenicol began to appear in the early 1950s, soon after, the first textbook on ADRs, was

published, these events among others gave rise to pharmacovigilance, the study of adverse effect of drugs.

- The 1960s were formative years for pharmaco-epidemiology.
- In 1966 one of the largest and perhaps the most famous pharmaco-epidemiology study, the Boston Collaborative Program began.
- Perhaps the most dramatic adverse consequence of drug use was reported in 1961 by McBride who identified Phocomelia in infants born to mothers who had taken the thalidomide Pharmacotherapy precipitated the first textbook on pharmacoepidemiology

□ Historical Backgroup:

- The pure Food and Drug Act, was passed in 1906 in response to excessive adulteration and misbranding of food and drugs available at that time.

• There were no restriction on sales or requirement for proof of efficacy or safety of marketed drugs.

• In 1937 over 100 people died from renal failure as a result of the marketing by the Massengill company of elixir of sulfanilamide dissolved in diethylene glycol.

• So preclinical toxicity testing was required for the first time, in addition, manufactures, were required to gather clinical data about drug safety and submit these data to the FDA before drug marketing. Little attention was paid to adverse drug reaction until the early 1950s.

• In 1952, the first book of adverse drug reactions was published in the same year, the AMA council on Pharmacy and Chemistry established the first official registry of adverse drug effects to collect cases of drug induced blood dyscrasias.

•In 1960, the FDA began to collect reports of ADR and sponsored new hospital based drug monitoring program.

•In the winter of 1961, the world experienced the infamous thalidomide disaster, in United Kingdom. this resulted in the establishment in 1968 of committee on safety of medicines.

•In 1962, the Kefauver-Harris Amendments were passed which is for proof of drug safety. In addition the amendment required the review of all drugs approved between 1938 and 1962, to determine if they too were efficacious.

•The mid-1960s also saw the publication of serious of drug utilization studies. Despite the more stringent praess for drug regulation, the late 1960s, 1970s, 1980s and specially the 1990s and 2000 have seen a series of major ADR.

•In 1980 the drug ticrynafen was noted to cause death from liver disease.

- In 1982, benoxaprofen was noted to do the same.
- Triazolam, thought by the Netherlands in 1979 to the subject to a disproportionate number of central nervous system side effects, was discovered by the rest of the world to be problematic in the early 1990s.

Human insulin was marketed as one of the first of the new biotechnology drugs, but soon thereafter was accused of causing a disproportionate amount of the hypoglycemia.

- Fluoxetine was marketed as a major new important and commercially successful psychiatric product, but then lost a large part of its market due to accusations about its association with suicidal ideation.

- Twenty two drugs removed from market since 1980s. Ex: Bromfenac (1998), Cerivestatin (2001) etc)

- B/W 1990 and 2004 at least 13 no-cardiac drugs were subjected to significant regulatory action because of cardiac concern including astemizole, droperido, rofecoxib.
- In 1996, guidelines for good epidemiology practice for drug device vaccine research in the U.S which was very recently updated errors that are not prevented, must be identified and corrected efficiently and quickly before they inflict harm, turning specially to medication.. from 2.4% to 6.5% of hospitalize patient suffer adverse drug event. prolonging hospital stages by 2 days and increase of cost of $2000-2600/Pt
- 7000 U.S death was reported -(1993)
- Finally, another major new initiative of close relevant to pharmacoepidemiology is risk management.
- There is increasing recognition that the risk/benefit balance of some drugs can only be considered acceptable with active management of their use, to maximize their efficacy or minimize their risk.

Aims And Applications of pharmacoepidemiology:

- Definition:

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

Aims:

- Pharmacoepidemiology aims to complete the evaluation of drugs made before approval, by providing reliable information concerning effectiveness, safety and utilization of medicines in realistic conditions...
- risk benefit assessment
- Aims at providing new information not available from premarketing studies like:
  - Discovery of previously undetected ADR and beneficial effects
  - Pattern of drug utilization
  - 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 pharmaco epidemiologic 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. Study of Drug Utilization:

It was defined by the world health organization as the marketing, distribution, prescription and use of drug in society and the resulting medical, social and economic consequencies.

→ 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.

→ To monitor the effects of informational and regulatory activities.

→ Estimate of disease prevalence

→ To estimate drug expenditures

- Clinical problems to be addressed by pharmaco epidemiologic research:

For a drug to be marketed it must be shown that it can effectively modify the natural course of disease or alleviate symptoms when used appropriately.

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2. Evaluating And Improve the Prescription:

- Factors responsible for sub optimal prescribing includes.

- Failure of clinician to keep abreast of new evidence
- Errors of omission
- Patient demand
- 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.

#Methodologic problems:

The ability to evaluate the effectiveness of DUR programs by means of randomize experiments is limited.

-Another problem is that when randomize experiment have been performed the need to keep the intervention and control groups free from cross contamination has necessitated the randomization of cluster rather than the randomization of individual patient.

4. Pharmacoepidemiologic Studies of Vaccine Safety:

Vaccines are among the most cost effective and effective public health interventions have led to

considerable decline in vaccines 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:

Regulatory agencies monitor the safety of devices by reviewing the adverse events reports from users, sponsors or the scientific literature.

2. Public health impact:

If epidemiologic evidence points to a safety problem with device further information is then require to evaluate the public health impact of doing nothing, taking an action or perhaps

taking an alternative action.

6. Studies of Drug Induce Birth Defects:

Teratogenesis is a unique adverse drug effects affecting an organism (the fetus other than the one for whom the drug was intended (mother).

Women of child bearing age were exclude from clinical studies because of concern about potential teratogenecity.

Premarketing clinical studies don't provide this information.

7. Pharmacoepidemiology and risk management:

- Goal of risk management is to enhance the safe use of medicines by optimizing the balance of benefit and risk.
- This can be accomplished by increasing the benefit and/or decreasing the risk associated with the use of drug product.
- The most common method use to attend to

improve the balance of benefit to risk of specific drug products include professional labeling and package insert, special letters send to health care professional and training programs.

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.
- It is possible now to detect many medication errors using large claims data basis

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 automated data bases include drug administered in hospital.
- Intensive hospital base surveillance consist of routine prospective recording of demography and clinical information on hospitalized patient including all drugs administered through out the hospital stay.

- 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.