PHARMACOVIGILANCE

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Outline

- Definitions
- History and Development
- Need and Objectives
- Classification of ADRs
- Serious ADR vs Severe ADR
- Causality Assessment

- **What is Pharmacovigilance ?**

  - Pharmakon (Greek) = Medicinal Substances
  - Vigilia (Latin) = To keep watch

- **WHO Definition:**

  “ The science & activities relating to the detection, assessment, understanding & prevention of adverse effects or any other drug related problems.”

Adverse event (AE):

- Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction (ADR):

- A noxious and unintended response that occurs at doses typically used in humans for disease prevention, diagnosis, therapy or the modification of physiological functions.

History and Development

1847

- Chloroform was used as an anesthetic agent during childbirth and surgery by James Young Simpson.

- After the use of chloroform, many deaths were reported due to “Chloroform-induced syncope”.

- **1880** :The British Medical Association formed the Glasgow Committee. They studied chloroform's effects and found it more harmful to the heart and riskier than ether for anesthesia.

1888 :Edward Lawrie claimed that chloroform could be safely used in many people without any deaths.

- This led to the creation of the First Hyderabad Chloroform Commission to check Lawrie's statement.

- After experiments on 141 animals, they concluded that chloroform could be safe for anesthesia if breathing was closely watched.

Second Hyderabad Chloroform Commission:

- However, the findings of the First Hyderabad Chloroform Commission were not universally accepted, particularly in England. As a result, a Second Hyderabad Chloroform Commission was established to reinvestigate.

- This commission included a representative from The Lancet, a renowned medical journal.

- The Second Hyderabad Chloroform Commission confirmed the conclusions made by the earlier Glasgow Committee, reiterating that chloroform was risky for use in anesthesia and posed significant dangers to the heart.

1897

- A German chemist named Felix Hoffmann resynthesized diacetylmorphine, which was later named 'heroin' due to its perceived heroic effects.

Felix Hoffmann

- It acquired the name Heroin because it was used to treat various medical conditions, from childhood coughs to war injuries.

- It was even utilized in attempts to cure morphine addiction, but it led to worsening addictions and increased tolerance levels to the drug over time.

- In 1910, around 500,000 people were found to be addicted to heroin.

- In 1913, Bayer Laboratory stopped the production of diacetylmorphine due to its addictive potential.

1937

- A scientist named Domagk used a dye containing sulfanilamide for his daughter, who was suffering from sepsis caused by Staphylococcus aureus.

Elixir sulfanilamide

- Following its success, a company named S.E. Massengill started the production of Elixir sulfanilamide, combining sulfanilamide with diethylene glycol.

- Patients who were given this product were found to have kidney damage, resulting in approximately 105 reported deaths.

1938

- In 1938, the Federal Food, Drug, and Cosmetic Act was passed.

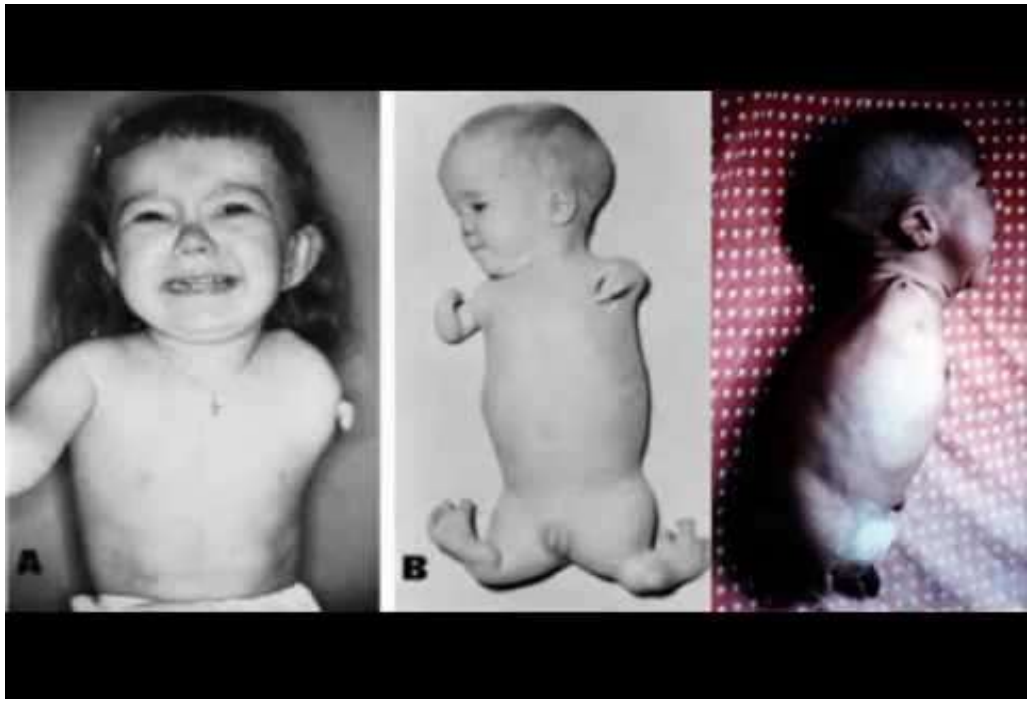
- Among its various provisions, the FD&C Act mandated that drug manufacturers must provide evidence of the safety of their products before marketing them.

- This requirement necessitated the submission of safety data and other relevant information to the Food and Drug Administration (FDA) for review and approval before drugs could be introduced to the market.

1954

- In France, a compound named Stalinon was used to treat staphylococcal infections, composed of Diiododiethyl ether with Vitamin F.
- However, it was later discovered that Stalinon was neurotoxic and resulted in approximately 102 deaths.
- After the incident in 1959, there were reforms in drug regulations and international marketing.

1961



Thalidomide disaster

- In Germany, a company named Chemie Grunenthal produced a product called Thalidomide, primarily introduced as a sedative and hypnotic medication.

- Later, some physicians found its usefulness in treating nausea and vomiting associated with the first trimester of pregnancy.

- Thalidomide was initially considered a safe and effective drug and was widely available without a prescription.

- Dr. William McBride in the Australia observed approximately a 20% increase in cases of phocomelia among patients using Thalidomide.

- A total of 12,000 cases were reported from Europe, Australia, and Canada combined.

- After the Thalidomide crisis, U.S. President John F. Kennedy passed an act named the 'Kefauver Harris Amendment Act,' which made it mandatory for companies to submit data on drug efficacy and safety before marketing in the USA.

1964

- The UK implemented the Yellow Card system for reporting adverse drug reactions.

- It enables healthcare professionals and the general public to report suspected adverse reactions or side effects associated with medicines, vaccines, herbal remedies, and other healthcare products.

- This system aids regulatory authorities in taking appropriate actions, including potential changes to product information, warnings, or even the withdrawal of medications if necessary, to ensure public safety.

In Confidence

YellowCard
COMMISSION ON HUMAN MEDICINES (CHM)

It's easy to report online at
www.mhra.gov.uk/yellowcard

MHRA

REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in the British National Formulary (BNF) or **www.mhra.gov.uk/yellowcard** for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS

Patient Initials:_____ Sex: M / F Is the patient pregnant? Y / N Ethnicity:_____

Age (at time of reaction):_____ Weight (kg):_____ Identification number (e.g. Practice or Hospital Ref):_____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S)

Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome
Recovered ☐
Recovering ☐
Continuing ☐
Other ☐

Date reaction(s) started:_____ Date reaction(s) stopped:_____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

☐ Patient died due to reaction
☐ Life threatening
☐ Congenital abnormality
☐ Involved or prolonged inpatient hospitalisation
☐ Involved persistent or significant disability or incapacity
☐ Medically significant; please give details:_____

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address:_____

Postcode:_____ Tel No:_____

Email:_____

Speciality:_____

Signature:_____ Date:_____

CLINICIAN (if not the reporter)

Name and Professional Address:_____

Postcode:_____ Tel No:_____

Email:_____

Speciality:_____

Date:_____

Information on adverse drug reactions received by the MHRA can be downloaded at **www.mhra.gov.uk/daps**
Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at **www.mhra.gov.uk/drugsafetyupdate**

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

1965

- The European Union issued EC(European community) Directive 65/65 with the primary goal of harmonizing pharmaceutical regulations across the member states to safeguard public health and ensure the quality, safety, and efficacy of medicinal products circulating in the European market.

1970

- Diethylstilbestrol (DES) is a synthetic estrogen that was prescribed to pregnant women between the late 1930s and early 1970s to prevent miscarriages and other complications during pregnancy.

- It was later discovered that Diethylstilbestrol (DES) was ineffective for its intended purposes and, moreover, had serious long-term health consequences for both the mothers who took it and their offspring.

- Diethylstilbestrol (DES) was found to be associated with various adverse health effects, particularly in the offspring exposed to the drug in utero.

- Some of the health issues reported among DES daughters include an increased risk of a rare form of vaginal cancer (clear cell adenocarcinoma), reproductive tract abnormalities, fertility problems, and an elevated risk of certain cancers such as breast cancer.

1989

- A study called the CAST (Cardiac Arrhythmia Suppression Trial) found that Class 1 antiarrhythmic drugs (encainide, flecainide) caused premature ventricular contractions leading to increased mortality.

- These drugs were informally termed 'PVC killers', referring to their association with premature ventricular contractions.

1993 :The MedWatch program was first launched by the U.S. Food and Drug Administration (FDA).

- It was established to provide healthcare professionals and consumers with a platform to report adverse events, product problems, and medication errors related to FDA-regulated products.

- MedWatch was introduced to enhance post-marketing surveillance and monitoring of the safety and effectiveness of drugs, medical devices, biologics, and other FDA-regulated products.

- Revised MedWatch and draft MedDRA (Medical Dictionary for Regulatory Activities) released by USA in 1999.

2007 : FDA amendment act was passed.

- Key components of the FDA Amendments Act of 2007 include:

- **Post-Market Surveillance:** FDAAA expanded the FDA's authority to monitor the safety of drugs after they enter the market by requiring additional post-market studies and clinical trials for certain medication.

- **Pediatric Research:** The act incentivized and promoted pediatric research by providing market exclusivity extensions for drugs studied in pediatric populations, thereby encouraging drug manufacturers to conduct studies in children.

- **Drug Labeling Authority:** The act empowered the FDA to require changes in drug labeling based on new safety information, allowing the FDA to mandate label changes even without the manufacturer's proposal.

- **Generic Drugs:** FDAAA aimed to streamline the approval process for generic drugs to facilitate their market entry while maintaining safety standards.

Need of Pharmacovigilance

1.Unreliability of preclinical safety data:

- Well-controlled conditions
- Small and specific sample size
- Pressure from various groups to reduce time to approval

2.Changing pharmaceutical marketing strategies

- Aggressive marketing
- Direct to consumer advertising
- Launch in many countries at a time

3.Changing physician and patient preferences

- Increasing use of newer drugs
- Shift of supervised to self-administered therapy

4.Easy accessibility

- Increasing conversion of prescription drugs to OTC drugs
- Easy access by internet
- Easy availability of complementary medicines
- Easy availability of substandard drugs

Objectives

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to the use of medicines.
- Contribute to the assessment of benefit and risk of medicines, encouraging their safe, rational and more effective use.

- Role of Pharmacovigilance:

1)To identify, quantify and document drug related problem.

2)To contribute to reduce the risk of drug related problems in healthcare system.

3)To increase knowledge and understanding of factors and mechanisms, which are responsible for drug related injuries.

Classification of Adverse Drug Reaction:

Type	Feature	Example	Management
A(Dose related)	•Predictable •Related to pharmacological action •Low mortality	•Hypoglycemia by insulin	•Reduce dose •Withhold the drug •Symptomatic management
B(Non dose related)	•Unpredictable •Not related to pharmacological action •High mortality	•Hepatitis by halothane	•Withhold the drug •Avoid in future
C(Dose and Time related)	•Uncommon •Related to cumulative dose	•Hypothalamic pitutary adrenal axis suppression by corticosteroid	•Reduce the dose •Withhold the drug
D(Time related)	•Uncommon •Usually dose related •Becomes apparent sometimes after use of drug	•Corneal opacities after thioridazine	•Often difficult to manage

Type	Feature	Example	Management
E(Withdrawal)	•Uncommon •Occurs after the withdrawal of drug	•Opiate withdrawal syndrome	•Reintroduce or •Withdraw slowly
F(Unexpected failure of therapy)	•Common •Often caused by drug interaction	•Oral contraceptive when used with Enzyme inducer	•Increase dosage

Detection of adverse drug reaction

- Premarketing safety evaluation
- Post marketing survillance
- Causality assessment
- Communicating ADR
- Postal survey method
- Dechallenge/Rechallenge

Serious Adr

- A serious ADR is any untoward medical occurrence that at any dose :

- ✓ Results in death
- ✓ Is life threatening
- ✓ Requires hospitalization or prolongation of hospitalization
- ✓ Results in persistent disability
- ✓ Causes congenital anomaly/birth defect

Severe ADR

- Modified Hartwig's Criteria:

1. An ADR occurs but requires no change in treatment with the suspected drug.

2. The ADR requires that the suspected drug be withheld, discontinued or changed.

3. The ADR requires that the suspected drug be withheld, discontinued or changed and/or an antidote or other treatment required.

4. Any level 3 ADR that increases length of stay by at least 1 day or the ADR is the reason for admission.

5. Any level 4 ADR that requires intensive medical care.

6. The ADR causes permanent harm to the patient.

7. The ADR either directly or indirectly leads to the death of the patient.

- Level 1-2 : Mild
- Level 3-4 : Moderate
- Level 5-7: Severe

Preventability criteria by Schumock and Thornton scale

- Definitely Preventable

1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5. Was there a known treatment for the Adverse Drug Reaction?

- Probably Preventable

6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventative measures not prescribed or administered to the patient?

- Not preventable

10. If all above criteria not fulfilled

Causality Assessment

- The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction.

When to assess causality?

- During clinical research, investigators participating in clinical trials are required to conduct causality assessment for all adverse events.
- When the report is initially received by the regulatory authority or a pharmaceutical company.
- At the time of signal generation from a number of suspected ADR reports.

Factors to be considered in causality assessment

- **Temporal relationship between drug administration and onset of reaction**:

  - A strong causal relationship is supported when the onset of an ADR coincides with the expected peak tissue concentration of the drug.

The Clinical and Pathological Characteristics of the Events

- For example, drug induced hemolytic anemia should be accompanied with increased bilirubin level and decreased hemoglobin level.

Pharmacological Plausibility

- As most ADRs are type A reactions (i.e., augmentation of pharmacological actions), the ADRs owing to a drug will most likely mimic its pharmacodynamic characteristics.

Preexisting Information about the ADR

- It is important to determine whether the AE has been previously reported as an adverse reaction (in clinical trials and postmarketing).

- Although the Summary of Product Characteristics /package insert, or the Investigator Brochure for products in clinical development, includes a list of AEs or suspected ADRs that have been previously reported, the search for important events may need to include information from sources (journals, databases, etc.) also.

Concomitant Medication and Underlying Concurrent Illnesses:

- Patients who are taking more than one drug, it is often difficult to decide which one is the more likely cause of the suspected ADR.
- Some events that are attributed to drug exposure may be simply manifestations of preexisting conditions.
- For example, anemia owing to zidovudine may be undistinguishable from anemia owing to HIV infection.

- **Response to Dechallenge and Rechallenge**
- **Patients' Characteristics and Medical History**
- **Drug Interactions**

Methods for causality assessment

- Broadly, these systems can be divided into three categories:

1. Unrestricted clinical evaluation/global introspection.

2. Algorithms, with or without scoring.

3. Bayesian probabilistic methods.

Unrestricted Evaluation/Global Introspection

- This is the most commonly used method by clinicians and by many pharmaceutical companies and regulatory authorities.
- Although the method is easy to apply and has a "common-sense" approach, it lacks objectivity and is subject to errors and fallacies.
- According to the WHO-UMC criteria, AE can be related with suspected drugs in the following manner:

1.Certain: If the clinical event or laboratory tests abnormality:

- ✓ Has plausible time relationship to drug intake
- ✓ Cannot be explained by underlying disease or other drugs
- ✓ Well-defined clinically and/or pathologically and pharmacologically
- ✓ Responds in a plausible manner to dechallenge and response to rechallenge if carried out is satisfactory.

2.Probable: If the clinical event or laboratory tests abnormality:

- ✓ Has reasonable time relationship to drug intake
- ✓ Cannot be explained by underlying disease or other drugs
- ✓ Response to drug withdrawal (dechallenge) is clinically reasonable
- ✓ Rechallenge has not been carried out.

3.Possible: If the clinical event or laboratory tests abnormality:

- ✓ Has reasonable time relationship to drug intake
- ✓ Can be explained by underlying disease or other drugs
- ✓ Information on drug withdrawal may be lacking or unclear.

4.Unlikely: If the clinical event or laboratory tests abnormality:

- ✓ Has an improbable (if not impossible) time relationship to drug intake
- ✓ Can be easily explained by underlying disease or other drugs

5.Unclassified: If the clinical event or laboratory tests abnormality:

- ✓ Requires more information for proper assessment or additional data are under examination.

6.Conditional: If the clinical event or laboratory tests abnormality:

- ✓ For which it is not possible to obtain additional information necessary for an appropriate evaluation.

Structured Algorithms, With or Without Scoring

- There are many structured or semi-structured algorithms for causality assessment.
- Whenever a structured method for causality assessment is properly used, no important point is likely to be missed.
- The most well-known and widely used algorithm is the one developed by Naranjo et al., which is popular for its simplicity and ease of use

Other algorithm based methods include:

- Karmer’s method
- Venulet’s method
- French method

Naranjo's algorithm

Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
TOTAL SCORE:				6

*A total score of 6 was calculated, which makes the adverse reaction "probable" for the drug under question

Bayesian Probabilistic Methods

- The Bayesian approach is based on assigning a prior probability to the AE under investigation.
- In drug safety, the prior probability of an adverse reaction is based on information obtained from premarketing clinical trials and epidemiological studies for patients with the underlying illness.
- That probability is then modified in the light of the information obtained from the new information (likelihood ratio). The revised probability is called the posterior probability (which if high, denotes causality).

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Thank You!