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An Overview Of Pharmacovigilance Knowledge And Reporting System Among Paramedical Students

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ABSTRACT

Adverse Drug Reaction (ADR) is a damage or injury response that is caused due to intake of a drug. The ADRs may arise after administration of a single dose, or long-term administration of a drug. It might also occur as a consequence of the administration of two or more drugs as a combination product or separately. The study of ADRs is known as Pharmacovigilance. The four pillars of Pharmacovigilance include detection, assessment, understanding and prevention of ADR. The prime objective of ADR reporting is that to identify safety of drugs followed by improving patient safety, evaluation of incidence of ADRs, identification of pre-disposing factors etc. The main purpose of the PV study is to protect the future generations or the potential users from the harmful effects of a drug that is already available in the market. The emanation of side effects resulting from the use of drugs are unavoidable. But the occurrence of morbidity and mortality as a result of ADR can be reduced if proper measures are promptly adopted by the local, as well as by the global regulatory organizations. Paramedics are life-savers in life-threatening situations. They should have fast-response and should be quick-witted, in such a way that the sick and injured patients may survive long enough to make it to the hospital or to a medical facility. Training on how to report an ADR, where to report, when to report can increase the rate of ADR reporting among paramedics and also reduce ADR related mortality thereby increasing patient safety.

KEYWORDS: Pharmacovigilance, ADR, Adverse drug reaction, Paramedics,

INTRODUCTION

The etymological roots for the word "Pharmacovigilance" are: *Pharmakon* (Greek) = medicinal substance, and *Vigilia* (Latin) = to keep watch. Pharmacovigilance (PV or PhV), also known as drug safety, is the pharmacological science and a pursuit relating to the collection, detection, assessment, monitoring, and prevention of adverse effects related to pharmaceutical products. According to WHO, adverse drug reaction (ADR) is defined as any response to a drug that is noxious and unintended and that occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.

Pharmaceutical and biotechnological medicines are outlined to cure, prevent or treat diseases however, adverse drug reactions (ADRs) can cause serious harm to patients. ADR notably affect the quality of life of the patient. It is hazardous to mankind. For example, side effect and drug allergy fall under ADR.

Pharmacovigilance is one of the important pillars of the healthcare system. They participate in assessment, monitoring and discovery of interaction among drugs and effect of drugs in human beings. Thus, ADR monitoring is having vital importance for safety of a medication. Challenges of maximizing drug safety and maintaining public confidence have become a necessity. Complex pharmaceutical companies must not only monitor, but also proactively estimate and manage drug risk throughout a products lifecycle, from its developing stage to post market drug safety monitoring; it is an essential part for the effective use of medicines and for high quality medical care. It has the possibility to encourage confidence and hope among patients and health professionals in medicines and contributes to raising quality of medical practice. Health care practitioners are in position to make good use of their patient's positive and negative experiences of treatment to contribute to medical science and to an improved understanding of disease and medicines.

A vital and complex relationship exist between wide ranges of partners in the practice of drug safety monitoring such as industry, hospitals, government, health care centres, patients etc.

Sustained commitment and collaboration are important if future challenges in Pharmacovigilance are to be met in order to improve and flourish.

The discipline of Pharmacovigilance has emerged considerably since 1972. It is critical to meet the challenges of the increasing range and potency of pharmaceutical and biological medicines that includes vaccines, which carry with them and inevitable and somewhat unpredictable potential to harm. The menace of harm, however is less when medicines are used by an informed health professionals and by patients, who themselves understand and share responsibility for their drugs. When toxicity and adverse

events appears, especially when previously unknown in association with the drugs, it is important that they are analysed and communicated effectively to a public that has the knowledge to interpreting the information. This is the role of Pharmacovigilance of which much has already been procured. But more efforts required for the integration of the discipline in to the clinical practice and public policy.[1]

Spontaneous reporting of ADRs and adverse events is the backbone of Pharmacovigilance system. Spontaneous report is an unprompted communication by healthcare professionals to regulatory authority, company or other organization that describes one or more ADRs in a patient who was given medicines and that doesn't derive from a study or any organized data collection scheme. Spontaneous reports place a vital role in the identification of safety signals of a marketed drug. Spontaneous reporting of ADRs is a vital tool for gathering the safety information for early detection. The advantage of spontaneous reporting that it is available immediately after a new product is marketed is continued indefinitely and cures all patients that receive the medicines. Spontaneous reporting is the most suitable method for detecting rare and new ADRs and frequently evolves safety signals which need to be examined further. It is a passive approach to Pharmacovigilance relying entirely on the motivation of individuals to report suspected ADR to a local or national Pharmacovigilance centre. Circumventing illness is a collective responsibility of industry, drug regulators, clinicians and other healthcare professionals to enhance their contribution to public health.

HISTORY

The earliest known records of Pharmacovigilance precede to ancient civilizations such as Egypt, Greece, and Rome, where doctors and healers recorded the effects of various medicinal plants and substances. These ancient healers used these records to identify which treatments were most effective and which had dangerous side effects. The history of Pharmacovigilance started almost 175 years ago, on Jan 29, 1848, when Hannah Greener from the Northern England died after receiving chloroform anaesthetic. Sir James Simpson had discovered that chloroform was a safer and powerful anaesthetic, and he had introduced it in clinical practice. The causes of Hannah's death were scrutinized to understand what happened to Hannah, but it was non-viable to identify what killed her. They came to a conclusion that she died probably due to arrhythmia or due to pulmonary aspiration. The Lancet Journal intimated a commission to take on this problem due to recurrent tragedy reports from clinicians. The commission appointed English doctors, including the doctor in colonies, to report deaths caused by chloroform anaesthesia. The results were published in "The Lancet" in 1893.

In 1883 Dr. Harvey Wiley commenced the campaign for the Federal law for Food and Drugs Act that was finally passed in 1906. The first practical international collaboration in drug monitoring started in 1968; the law was further strengthened by the following incidents such as the poisoning of children by

"Sulphanilamide" and the "Thalidomide" tragedy. In particular the thalidomide tragedy changed the system of Pharmacovigilance.

One of the earliest examples of modern Pharmacovigilance was the establishment of the Therapeutic Index in the United States in the 1920s. This index was used to evaluate the safety and efficacy of drugs. It served as a foundation for the implementing modern drug safety system and methods. The spontaneous reporting of ADR became systematic, organized, and regulated.

In 1938, Federal Food, Drug, and Cosmetic Act (D&C) was implemented.

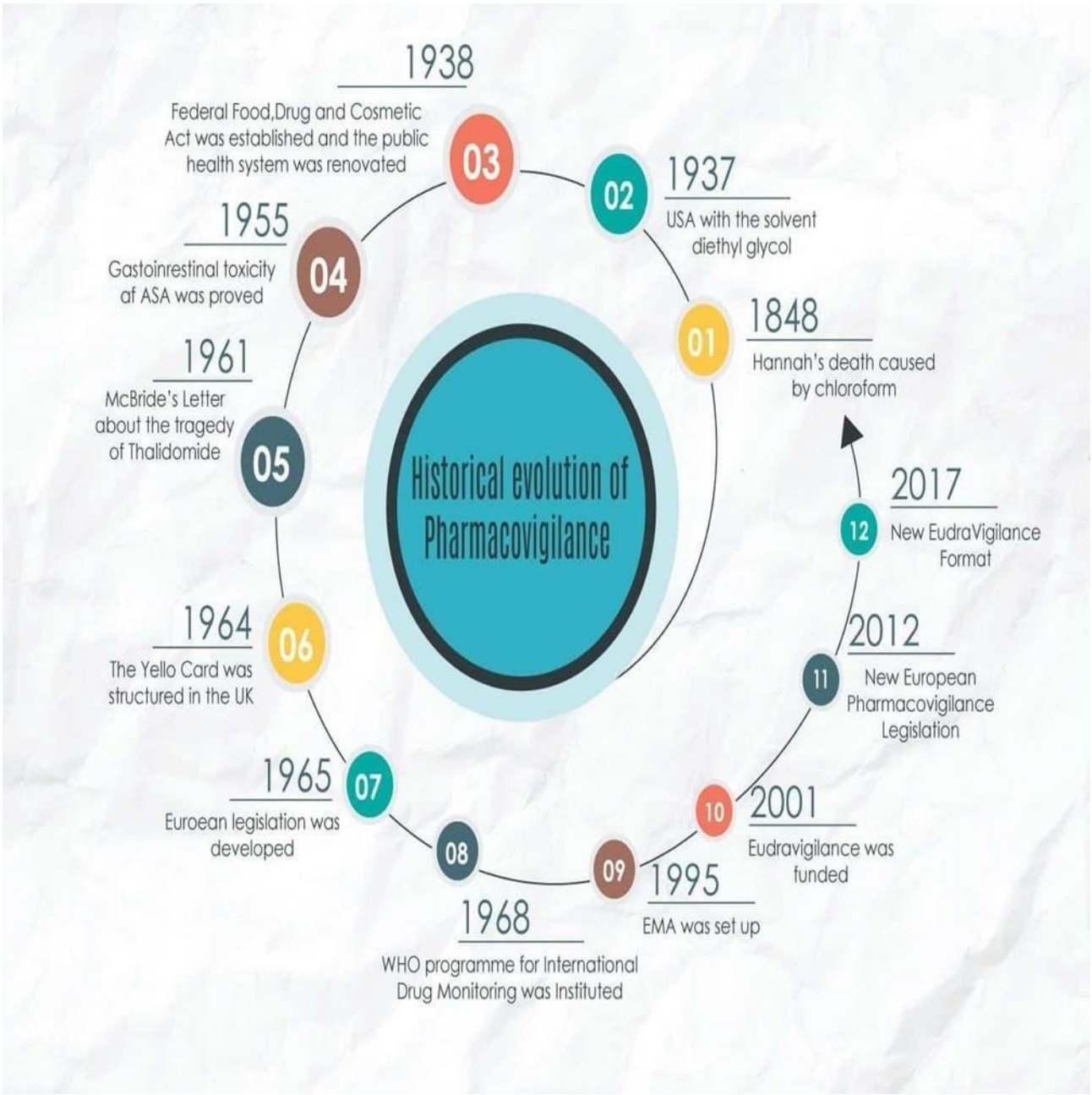


Fig 1: History of Pharmacovigilance

In 1968, the WHO Programme for International Drug Monitoring was instituted and ten members participated in this program (Australia, UK, USA, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and Netherlands). Italy participated in this program in 1975. In 1995, the European Medicines Agency (EMA) was set up. In 2001, EudraVigilance was founded. It is the official European database established solely for the management and analysis of information regarding suspected adverse reactions to medicines that have been authorized for sale in market or for clinical studies in Europe.

AIM OF PHARMACOVIGILANCE

- Improve patient care about the drugs and keep the patient safe from adverse effects of drug.
- Pharmacovigilance keeps track of any drastic effect of the drug.
- To research the efficacy of the drug and check effects of drugs during trials to the pharmacy and then keep monitoring their effects for many years.
- Bring improvement in the public healthcare system by a thorough assessment of drugs effect on the body.
- Promote training and knowledge about this field of medicine.
- To know the mechanisms of the drug inside the human body.
- To encourage safe and rational use of medicines.

OBJECTIVES OF PHARMACOVIGILANCE

- To detect unknown ADR and drug interactions properly and rapidly.
- Dissemination of information regarding ADRs, so that their frequency of occurrence can be reduced significantly.
- To identify mechanisms that cause an ADR and also to tackle the situation wisely.
- To rectify Therapeutic errors.
- Revaluation of the risk-benefit balance of medicine, so we can effectively use those drugs for a patient having more benefits and fewer side effects.

PURPOSE OF PHARMACOVIGILANCE

Pharmacovigilance has developed and will continue to develop in response to the special needs.

The concerns of Pharmacovigilance include the following:

- Herbals
- Traditional and complementary medicines
- Blood products and biologicals
- Medical devices
- Vaccines

Other issues of relevance to the science includes substandard medicines, medication errors, inadequate efficacy reports, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, adverse interactions of medicines with chemicals, other medicines and food.

VARIOUS PHARMACOVIGILANCE SERVICES

Fig 2: Importance of Pharmacovigilance

MAIN AREAS OF PHARMACOVIGILANCE

Pharmacovigilance is a huge and encompassing discipline.

It can be broadly divided into four main sub-specialisms:

Operations:

This sector mainly focuses on drug safety careers where many professionals begin their careers. Typical jobs under this sector include case processor, drug safety officer, drug safety associate, drug safety manager team lead and directorships. They are involved in collection and recording of information during pre-clinical and clinical trial sessions. They are also involved in collation of real-world evidence of ADRs reported by doctors and patients.

Surveillance:

In this sector, Professionals are concerned with surveillance activities like risk management, signal detection jobs. They create Development Safety Update Reports (DSUR) for drugs undergoing clinical trials and Periodic Benefit Risk Evaluation Report (PBRER) for post-market drugs. These reports are essential for the team to step into a conclusion on safety and efficacy of drug candidate. They also analyse the data collected by wider division

Systems:

This sector is involved in building and development of sturdy and inventive system. They are used to store and to allow access to immeasurable amount of safety data. The data can be accessed by all.

Qualified Person for Pharmacovigilance (QPPV)

QPPVs jobs are mainly concerned with marketed drugs and those about to be authorised. These are senior Pharmacovigilance roles that are filled only by very experienced professionals. This is a highly strategic appointment and one of great importance.

ADVERSE DRUG REACTIONS

Schatz et al (2015) described an ADR as "An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use"[2]. An adverse drug reaction (ADR) can be defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and

warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.[3]

Signs and Symptoms of ADRs

The signs and symptoms of ADRs include the following:

Mild symptoms: These include red, itchy, flaky, or swollen skin. Manifestations can also include flat, red area on skin which is covered with small bumps. Hives might be present.

Severe symptoms: It includes skin that blisters or peels, visual disturbances, severe swelling and itching. It can also cause conditions like toxic epidermal necrolysis that are severe.

Anaphylaxis symptoms: It includes throat tightness, trouble breathing, tingling, dizziness, and wheezing. Anaphylaxis is a life-threatening, sudden condition which requires immediate treatment.

Diagnosis of ADRs

1. **Patch test**: In this a small amount of the drug is put on the skin and the area is covered with a patch for 2 days. After 2 days the skin is examined by physician for any signs or symptoms of ADR.
2. **Skin prick**: This test uses a small quantity of drug that is applied on the forearm region followed by pricking skin with a needle.
3. **Intradermal test**: In this a small amount of liquid containing the drug is applied under the surface of your skin. Healthcare provider will watch for a reaction.
4. **Drug Provocation test**: It is also known as a challenge test. Drug is given in increasing doses by healthcare provider.

CLASSIFICATION OF ADR

In 1977, Rawlin and Thompson classified ADRs into "dose-related" and "not dose-related", which were designated "Type A" and "Type B". The same authors 4 years later in 1981 decided to rename these as "Augmented" and "Bizarre", followed by addition of other categories in later years.

Class	Description	Examples
Type A (Augmented)	ADRs are related to the pharmacological properties of the medicine. Dose related. The ADR are attributed to genetic variations e.g. hepatic and glomerular disorders	Nephrotoxicity caused by aminoglicosides Anticholinergic effects of tricyclic antidepressants
Type B (Bizarre)	Adverse reactions unforeseen and unpredictable ADRs have less or No relationship with the dosage.	Penicillin induced urticaria.
Type C (Chronic)	The cumulative toxic effects of a drug used over time. Chronic in nature and include the adaptive changes and the withdrawal effects. (dose related and time-related)	Hyperadrenocorticism in chronic corticosteroid use
Type D (Delayed)	Reactions that appear after sometime of the treatment. time-related	secondary cancers caused by use of Alkylating agents e.g. cyclophosphomide
Type E (End of use)	ADRs occurring on sudden termination of treatment	Convulsions as a result of stopping anticonvulsants

Table 1: Classification of ADR

ADR classification based on severity:

- **Minor:** No treatment or antidote required.
- **Moderate:** Drug is not necessarily discontinued.
- **Severe:** Drug is discontinued due to potential life-threatening event.
- **Lethal:** ADR which has the potential to cause death.

ADR classification based on Onset of Event:

Depending on onset of event:

- **Acute**: Less than 60 minutes
- **Sub-acute**: 1-24 hours
- **Latent**: Greater than 2 days

Depending on whether they could take place in any patient, or in a specific susceptible population:

- **Reactions that might take place in anyone:**

Drug overdose, Drug side effect, Drug interaction

- **Reactions that take place only in susceptible individual:**

Drug intolerance, Drug idiosyncrasy, Drug allergy, Pseudo allergic reaction

Others

- Secondary effects
- Toxic effects
- Photosensitivity
- Teratogenicity
- Mutagenicity
- Carcinogenicity
- Drug induced disease
- Drug dependence

DETECTION OF ADVERSE DRUG REACTIONS

The pharmaco-epidemiological methods are used now days to detect new signals of possible adverse drug reactions (ADRs) and these methods can either be 'hypothesis generating' where the aim is to detect new & previously undetected ADRs with a new drug or 'hypothesis testing' where these methods aim to prove whether any suspicions that may have been raised are justified.

Hypothesis generating methods include

- **Spontaneous ADR Reporting**- which is a system whereby any suspected ADRs are voluntarily notified by health professionals, pharmaceutical companies and other stakeholders to a central authority (Central Drugs Standard Control Organization -CDSCO in India).
- **Prescription Event Monitoring**- represents a method which is hybrid of spontaneous reporting with aspects of formal epidemiological studies.
- **Systematic methods**- public health surveillance data such as death registries are used to identify patterns of reactions that might be associated with drug use.

Hypothesis testing methods include

- **Case-Control Studies**- In case control studies, the it compares the exposure rate in the cases with the exposure rate in the control.
- **Cohort Studies**- These studies involve a group of patients (cohort) followed up for a time duration long enough to detect the outcome of interest.
- **Randomized Controlled Trials**- These studies involve patients divided into two groups randomly into exposed and the other not exposed, so that the outcomes can be compared.

REPORTING OF ADVERSE DRUG REACTION

Who can report?

- Health care professionals which include doctors, nurses, pharmacist.
- Non healthcare professionals including consumers and patients.

What should be reported?

If a patient is suspected to have an Adverse drug reaction, it should be reported via ADR reporting forms. ADRs resulting from prescription medicines, herbal remedies, and OTC medications can all be reported.

- In case of new drugs all ADRs are reported including the minor ones.
- For well-known medicines report all serious or unusual suspected adverse reactions.
- If an increased frequency of a given reaction is suspected.
- All suspected ADRs associated with drug-drug, drug-food or drug-food supplements (including herbal and complementary products) interactions.
- All suspected ADRs are associated with medicine withdrawals.
- ADRs occurring from overdose or medication error.
- ADRs in special fields of interest such as medicine abuse and medicine use in pregnancy (teratogenicity) and during lactation.
- In children under the age of 18, all suspected ADRs occurring, should be reported regardless of whether the medicine is licensed for use in children.

Children are often not exposed to medicines during clinical trials and many medicines are used in children even if they are not licensed for this purpose. This means that monitoring of medicine safety is particularly important for this age group.

How to obtain the reporting form?

At each hospital a Pharmacovigilance coordinator is assigned (preferred to be the clinical pharmacist, or the medicine information specialist), who is in charge of ADR related matters. For the hospital health care professionals, the reporting forms are available at the hospital Pharmacovigilance coordinator. Special stand for ADR reporting forms is available in the community pharmacies (mainly for patients, community pharmacists & may be for the nearby private clinics).

How to submit ADR report?

After filling the ADR reporting form; All ADR reports can be sent to the nearby ADR monitoring centre by:

- **On-line**: through website
- **E-mail**: special account for ADR reporting
- **By Hand**: contact person in hospitals, by pharmaceutical distribution companies

What happens to the reported ADRs?

1. The information obtained from the report will be used to promote safe use of medicines in the local, national and international levels
2. The submitted report will be entered into the national database of adverse drug reactions and be analysed on a regular basis. A well - completed and duly submitted ADR reported may result in:

- Additional investigations into the use of the medicine
- Appropriate changes in the package insert
- Change the schedule of the medicine
- Enhancing educational initiatives to improve the safe use of that medicine
- Other regulatory and health promotion interventions as the situation may warrant including withdrawal / recall.

COMPONENTS OF ADR REPORTING FORM

A suspected ADR reporting form contains following information

- Patient initials: name of the patient, age, sex, weight, date of birth.
- Details on suspected ADR reaction: date of onset, description of reaction.
- Details on suspected drug: route of administration of drug, dose, batch no, expiry date.
- Reporter information: Name, signature, address, email.

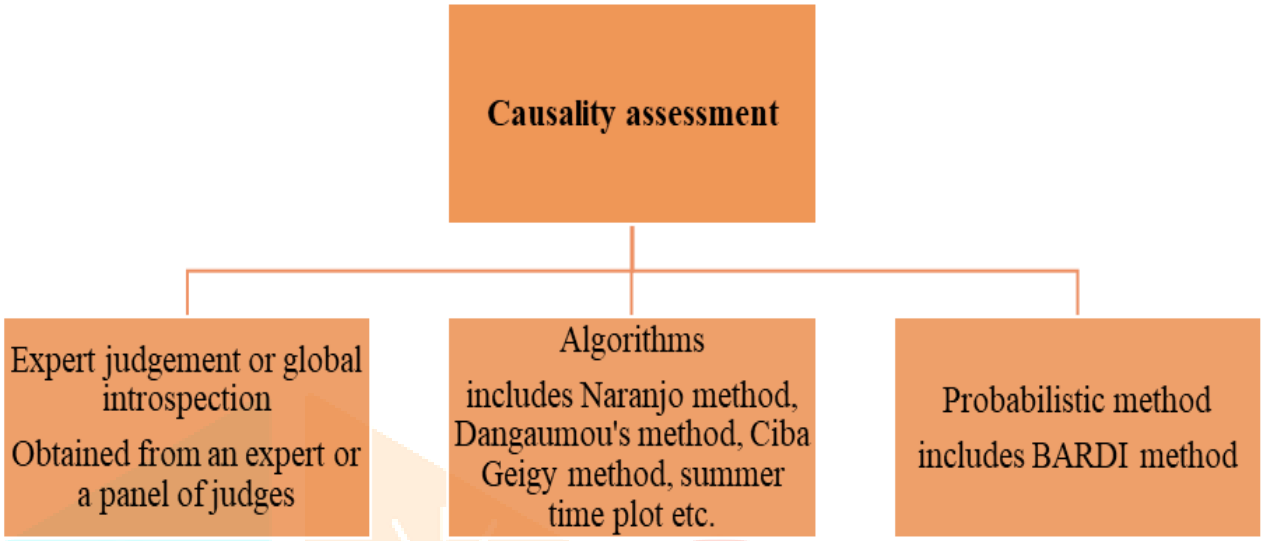
CAUSALITY ASSESSMENT

Causality assessment is the method of assessing relationship between a drug treatment and occurrence of an Adverse Drug Reaction.

Objectives of Causality Assessment:

- Signal detection
- Provide relationship between drug and ADR
- Better evaluation of benefits/harm profile of drugs.

Methods of Causality Assessment:



ROLE OF PARAMEDICAL PROFESSIONALS IN ADR REPORTING

Paramedics play an important role in helping people receive medical care during an emergency situation. They undergo extensive training and education in medicine, emergency procedures and medical technology, allowing them to make quick life-saving decisions even at the time of ADR emergencies and assist patients immediately on site.

PHARMACOVIGILANCE IN INDIA

Pharmacovigilance in India commenced way back in 1986. A formal adverse event monitoring system was established under the supervision of Drugs controller of India. India later joined WHO international drug monitoring programme in 1988. The partnership was a failure and ineffectual to achieve the objectives of the programme.

The National Programme of Pharmacovigilance was launched in 2005. It was renamed as Pharmacovigilance Programme of India (PvPI) in 2010. National coordination centre was shifted from New Delhi to Indian Pharmacopoeia Commission in Ghaziabad. The PvPI works to safeguard the health of the Indian population. It ensures that the benefit of medicines outweighs the risks associated with their use. As a part of PvPI, they established 250 adverse drug monitoring centres all across India. It has

also provided training to healthcare professionals regarding ADR monitoring. In addition to detection of substandard medicines and prescriptions, it also monitors dispensing and administration errors which ultimately leads patient confidence and safeguarding of public health. IPC-PvPI has now become a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services.

Challenges faced by PvPI

- Monitoring of generic drugs
- Monitoring of Biosimilars
- Monitoring of disease specific ADRs of ant diabetic drugs, cardiovascular drugs, antipsychotic drugs etc.
- Creating awareness in continuous basis.

Challenges addressed by PvPI

- Counterfeit drugs
- Antimicrobial resistance
- Surveillance during mass vaccination programmes
- Other national programmes

Current Scenario of Pharmacovigilance in India:

India is a developing country. There are more than 6,000 licensed drug manufacturers and over 60,000 branded formulations in India. India places itself at fourth position as the largest pharmaceutical producer in whole world. Nowadays, there is a rapid emergence of newer drugs in Indian industry. As a part of this concerns regarding drug safety is also increased. The need for the improvement of Pharmacovigilance system has increased considerably overtime. Indian based pharma companies have increased their potential to develop and launch new pharmaceuticals through their own research efforts and this has increased the importance of developing adequate internal Pharmacovigilance standards to detect adverse drug events. However, what is essential along with the funding is a focus on mission and effective strategy for developing the Pharmacovigilance systems, especially in the Drug Controller General of India (DCGI) Office, which is lacking. In older times, Pharmacovigilance was never done in Indian Pharmaceutical companies, be it Indian or Multi-National Companies (MNCs). Thus, there is an immense shortage of people who are educated in pharmacovigilance and who could be able to advice

the DCGI on this matter. Pharmacovigilance is a very complex subject, intertwined with many regulations and complex systems. Therefore, the need to engage a completely independent adviser who has extensive and practical knowledge on Pharmacovigilance, who can act as Pharmacovigilance Advisor to the Government of India to effectively implement the systems and policies on Pharmacovigilance Understanding by healthcare professionals and knowledge and motivation for Pharmacovigilance is almost negligible. In India, several consumer groups encourage patients to report any ADRs encountered by them, although there is no information for patients on how to report ADRs directly to the regulatory authority Direct reports from the patients, the ones who actually experience ADRs, are not accepted by the monitoring centres and by regulatory authorities. With many clinical trials and other clinical researches that conducted in India to understand the importance of Pharmacovigilance. At present, the DCGI should quickly access Pharmacovigilance so as to emerge as a Good Pharmacovigilance.

Currently India is considered to be a major centre for clinical research. The DCGI has shown significant involvement in ensuring safe usage of drugs. It is done by establishing the National Pharmacovigilance Program which is extended to Consumers, healthcare professionals, Nongovernmental organizations as well as hospitals. Hospitals should intentionally prepare and report suspected ADRs actively without any delay. They should participate in National Pharmacovigilance Program which ultimately ensures that the citizens of India receive safe and quality medicines. With the immense hard work and proper coordination of all stakeholders, we can definitely build a world class Pharmacovigilance system in India. It may result in tremendous advancement in this field.

FUTURE TRENDS IN PHARMACOVIGILANCE

Pharmacovigilance is expected to be a major argot in the near future.

Future of PV depends on the capability of direct engagement with patients and patient groups. They should be connected through their preferred communication channel to collate questions and concerns. It also helps in more effective translation of safety related information to the layperson. This will involve new ways of working internally as well as increased engagement with functions like patient advocacy, medical affairs, medical communications, and commercial to ensure a holistic view of the end customer.

The main goal of Pharmacovigilance is to ensure drug safety. Companies spend millions on Pharmacovigilance every year aiming to achieve drug safety but still Adverse drug reactions (ADRs) remain a major cause of death. In fact, 10-20% hospital admissions are due to ADRs. Huge number of resources are required for handling a single case. At the end of the day, the pharmaceutical companies will have no choice, but to migrate to an automated case-processing model in the upcoming years. According to the public opinion, pharmaceutical companies are the most distrusted. To influence

the society, pharmaceutical companies should be truthful. They should build trust and confidence among consumers. Advanced and sophisticated solution are available which have the capability to extract automatically, process and finally code the ADR data. Newer tools will increase the transparency across the pharmaceutical companies. It helps in promoting impartial comparisons between alternative pharmaceutical products. This is lead to more and more collaborations trust and finally lesser ADR. The signal management tools will automatically identify the analogues based on logical constructs like therapeutic area, drug class and less intuitive factors [4]

Furthermore, the safety profiling of medicinal products and the evaluation of the benefit-risk balance historically have been conducted. This information does not represent a diverse population. Underrepresented groups lead to knowledge gaps regarding safety between trials and real-world scenarios with an impact on confidence in medicinal products and latent unforeseen consequences for the impacted patient group. In future PV will play a major role in eliminating gaps in trial diversity.

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