



From Ensuring Patient Safety to Adverse Event Reporting: A Comprehensive Review on Pharmacovigilance

Mohd Abdul Muneim Farzaan, Md. Abdul Hafeez

MESCO College of Pharmacy

ABSTRACT

Pharmacovigilance (PVG) plays a crucial role in safeguarding drug safety and safeguarding patients from adverse drug reactions (ADRs) in India. While Pharmacovigilance is still in the developmental stages, there is a pressing need for significant progress in the reporting and management of ADRs. This practice involves monitoring drug interactions and their impacts on the human body. Adhering to Good Clinical Practices (GCP) and International Council for Harmonization (ICH) guidelines is essential for the effective implementation of PV in India, which is now recognized as the third largest pharmaceutical producer globally. The country has witnessed a rise in awareness regarding Adverse Drug reactions as a result of Pharmacovigilance initiatives.

The World Health Organization (WHO) emphasizes that Pharmacovigilance is instrumental in detecting, assessing, understanding, and preventing adverse effects and other drug-related issues. With the growth of clinical trials and research activities in India, it is imperative to understand and implement robust Pharmacovigilance systems to ensure drug safety. This review highlights strategies aimed at establishing and sustaining effective Pharmacovigilance frameworks to regulate and enhance drug safety measures. The focus is on promoting transparency and involving patients in the process.

Key Words: Pharmacovigilance, Adverse Drug Reactions, Drug Safety, Good Clinical Practices, Patient Involvement

INTRODUCTION

Pharmacovigilance (PVG) encompasses the comprehensive examination of Adverse Drug Reactions (ADRs). The term “Pharmakon” refers to “Drug,” while “Vigilance” pertains to “keeping watch or staying alert.” According to the World Health Organization (WHO), Pharmacovigilance is defined as “the science and activities focused on detecting, assessing, understanding, and preventing adverse effects or any other potential drug-related issues.”

In recent developments, patient perspectives have been integrated into pharmacovigilance practices, including ADR reporting, signal detection and evaluation, risk management, medication error assessment, benefit-risk assessment, and risk communication. Adverse drug reactions (ADRs) pose global challenges in both developing and developed countries, significantly contributing to morbidity and mortality. A meta-analysis published in 1998 ranked ADRs between the fourth and sixth leading causes of death in the US.

These adverse drug reactions not only impact patient well-being but also lead to increased morbidity, mortality, and financial burdens on society. Establishing a causal relationship between the drug and the event, known as causality assessment, is crucial but challenging. Causality assessment involves evaluating the likelihood that a specific treatment caused an observed adverse event by assessing the relationship between a drug treatment and the adverse event. This assessment is a vital aspect of pharmacovigilance, aiding in the improved evaluation of the risk-benefit profiles of medicines and the assessment of ADR reports in early warning systems and for regulatory purposes.

Historical Background of Pharmacovigilance:

Various significant incidents throughout history have underscored the dual nature of drugs, highlighting their potential to heal as well as harm. Examples include the tragic sudden death caused by chloroform anesthesia in 1877 and the fatal hepatic necrosis resulting from arsenicals in 1922. The enactment of the Food, Drug, and Cosmetic Act, along with the Kefauver-Harris Amendments, granted the FDA the authority to approve or reject the introduction of new drugs and the ongoing marketing of established medications based on robust evidence of their therapeutic effectiveness and safety.

By approximately 1980, many countries mandated the recording of adverse drug reactions, leading to continuous monitoring of the risks and benefits of products during both the investigational phase prior to authorization and post-marketing surveillance after commercialization. This vigilance has resulted in numerous instances of drug recalls or precautionary measures due to the identification of potential hazards during their use. Noteworthy examples include practolol and mucocutaneous syndrome, benoxaprofen and hepatic disorders/deaths in the elderly, temafloxacin and hemolytic anemia,

fenfluramine/phentermine and valvulopathy or pulmonary hypertension, terfenadine or cisapride and potential cardiac arrhythmias (especially when interacting with other agents), cerivastatin (Lipobay) and rhabdomyolysis, as well as increased risk of cardiovascular events.

The Erice Declaration on Communicating Drug Safety in 1998 prompted improved communication and information sharing among the industry, regulatory bodies, and the public. This progress was further reinforced by the establishment of the Eudravigilance Database in London in December 2001.

Historical milestones in pharmacovigilance include James Lind's first reported clinical trials in 1747 demonstrating the efficacy of lemon juice in preventing scurvy, the tragic death of 107 children due to sulfanilamide toxicity in 1937, reports of aplastic anemia linked to chloramphenicol in 1950, the global disaster caused by thalidomide toxicity in 1961, and the recognition of the importance of prompt action on adverse drug reactions by the 16th World Health Assembly in 1963. In 1996, India began conducting clinical trials adhering to global standards and joined the WHO Adverse Drug Reaction Monitoring program. Subsequently, pharmacovigilance was initiated in India in 1998, leading to the establishment of the National Pharmacovigilance Center in 2002. The National Pharmacovigilance Program was launched in India in 2004, followed by the implementation of structured clinical trials in 2005. The Pharmacovigilance Program of India (PVPI) was initiated in 2009-2010, marking significant progress in monitoring drug safety within the country.

Pharmacovigilance aims to achieve various objectives to enhance patient care and safety in the context of medication and medical interventions. These objectives include researching the effectiveness of drugs and monitoring their adverse effects from the laboratory to the pharmacy and beyond. By tracking any significant effects of medications, pharmacovigilance contributes to improving public health and safety. It also plays a crucial role in assessing the benefits, risks, and effectiveness of medicines, promoting their safe and rational use, as well as encouraging cost-effective practices.

Furthermore, pharmacovigilance strives to enhance education, training, and communication in the field to ensure that information about drug safety is effectively conveyed to the public. It also aims to increase protection for individuals using new medications and endorse transparent communication within communities. Additionally, pharmacovigilance supports the rational and safe utilization of medicines by continuously monitoring their efficacy and adverse effects. Overall, these objectives underscore the importance of pharmacovigilance in safeguarding public health and optimizing the use of medications.

Pharmacovigilance plays a critical role in ensuring the safety and monitoring of various types of medicines, including complementary and traditional medicines, vaccines, and biological medicines. This involves receiving, processing, and reporting adverse event reports, as well as following up with reporters to gather additional details about reported cases. Pharmacovigilance also provides information services to healthcare professionals and patients regarding product safety and offers safety expertise to internal cross-functional colleagues.

In the realm of good pharmacovigilance practices, it is essential to assess the benefit-risk balance of a product, develop tools to minimize risks associated with its use, evaluate the effectiveness of these tools, and continuously reassess the benefit-risk balance. Adjustments to risk minimization tools are made as necessary to further enhance the benefit-risk balance.

Partnerships are crucial in the field of pharmacovigilance, with various stakeholders playing key roles in drug safety monitoring. These partners include government entities, industry representatives, hospitals, academia, poison information centers, health professionals, patients, consumers, media outlets, and organizations such as the World Health Organization (WHO). Collaborative efforts and sustained commitment among these partners are essential to address future challenges in pharmacovigilance effectively and foster its continued growth and development.

GOOD PHARMACOVIGILANCE PRACTICES:

- Assessing a product's benefit-risk balance
- Developing and implementing tools to minimize its risks
- Evaluating tool effectiveness and reassessing the benefit-risk balance
- Making adjustments as appropriate to the risk minimization tools to further improve the benefit risk balance.

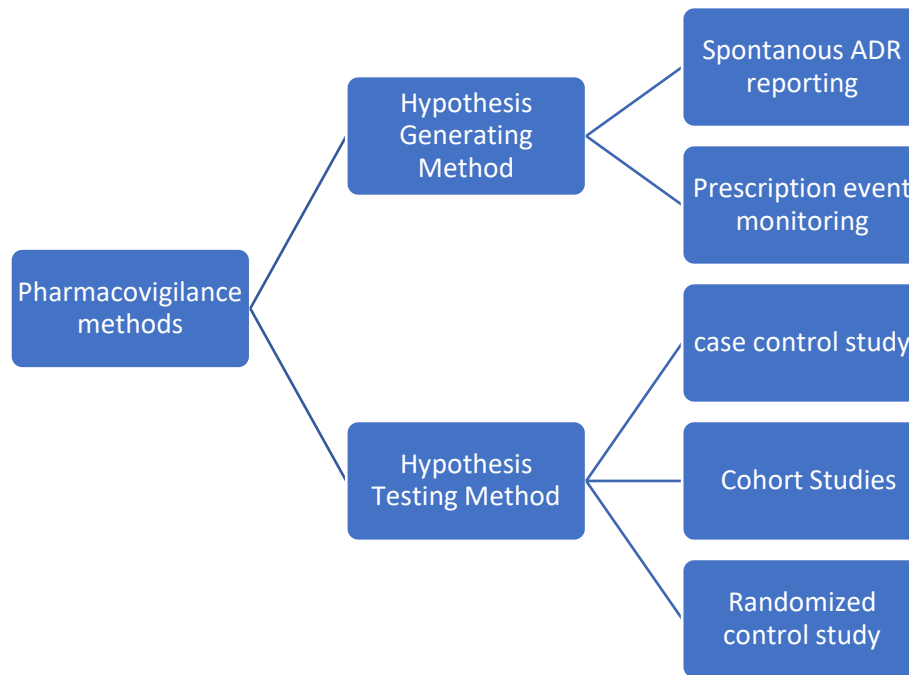
PARTNERS IN PHARMACOVIGILANCE

A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring. Sustained collaboration and commitment are vital if future challenges in pharmacovigilance are to be met in order to develop and flourish

- Government
- Industry
- Hospital and academia
- Poison information centers
- Health professionals

- Patients
- Consumers
- Media
- WHO (World Health Organization).

Methods of Pharmacovigilance



- Spontaneous reporting systems (SRSs) are a method of recording and reporting clinical observations of suspected Adverse Drug Reactions (ADRs) associated with a marketed drug. This reporting system is also known as spontaneous or voluntary reporting and has slight variations among different countries. The primary goal of SRSs is to monitor the safety of medicines. Physicians, pharmacists, nurses, and consumers use standardized forms to report alleged adverse drug reactions to regulatory systems.
- Prescription-event monitoring (PEM) is a non-interventional form of pharmacovigilance that involves observational cohort studies. In PEM studies, exposure is collected from a centralized service, and outcomes are obtained from simple questionnaires completed by general practitioners. Follow-up forms are used for selected Adverse Events (AE), and PEM captures all AE and suspected ADRs. The distribution of the number of AE per person depends on the nature of the drug under study.
- Dangaumou's French method has been used by the French government agency since 1977 to evaluate the causality of ADRs. This method separates intrinsic immutability (possible correlation between abused substance and dispassionate event) from extrinsic immutability (bibliographical data) using seven criteria, three connected and four semiological. The criteria include drug challenge, dechallenge, rechallenge, semiology (clinical signs), favoring component, arbitrary non-drug related, and laboratory tests. Scores are grouped as possible and dubious.
- Kramer et al. method This method applies when the offending drug is administered and a single adverse drug event has taken place. Each adverse event is assessed independently and assessment is prepared. One of the advantages of this algorithm is its transparency. However, certain levels of experience, expertise, and time are required to use this method effectively.
- Naranjo et al. method (Naranjo scale) It is utilized to verify causality in a variety of clinical situations utilizing the categories and definitions of definite, probable, possible, and doubtful. It consists of ten questions which are answered as yes, no and unknown. The event is assigned to a probability category predicated on the total score after totaling. A total score of ≥ 9 is definite, probable is 5-8, possible is 1-4 and doubtful ≥ 0 . This scale is more powerful when the adverse event is associated with only one drug, but when multiple drugs are involved or there is any interactions between drugs, this scale fails to identify the offending agent.

Balanced assessment method

This method evaluates a case report on various visual analog scale (VAS) models that each criterion is fulfilled individually. It has an added advantage that it considers an alternative causative factor as a possibility and not just as a separate factor. Each case is assessed independently by different assessors and the evaluation depends on the assessor's skills knowledge.

- Ciba-Geigy method

Expert consensus meetings have resulted in Ciba-Geigy method. Experts used their clinical judgment to assess adverse drug events and assign causality on a VAS. This method uses a checklist which is composed of 23 questions,

This is split into three sections:

- (i) History of present adverse reaction,
- (ii) patient's past adverse-reaction history, and
- (ii) Monitoring-physician's experience.

This updated method was found to have a high degree of agreement (62%) when compared with evaluator's assessments.

- Loupi et al. method

This method developed to assess the teratogenic potential of drug. The first sections of the algorithm sanction for the drug to be omitted if not implicated in the inception of the abnormality. The second section weighs the bibliographical data. The three questions consider alternative etiological candidates other than the drug; chronology of the suspect drug and other bibliographical data, to arrive at a conclusion on causality.

- Roussel Uclaf causality assessment method

This method is used in disease states such as liver and dermatological problems. A retrospect assessment of the reproducibility of this method among four experts had showed a 37-99% agreement rate.

- Australian method [18] Australian method involves the evidence which helps in to draw the conclusion, such as timing, and laboratory information from case reports presented and the antecedent cognizance on the suspect drug profile is deliberately omitted in the assessment.

STEPS IN PHARMACOVIGILANCE PROGRAMME



ADVERSE DRUG MONITORING: Adverse drug reactions (ADRs) are common, often unrecognized and typically under-reported. However, update knowledge and skills related to detection, assessment, prevention, management and transparent notification / reporting of ADR is essential for an efficient Pharmacovigilance everywhere on the globe.

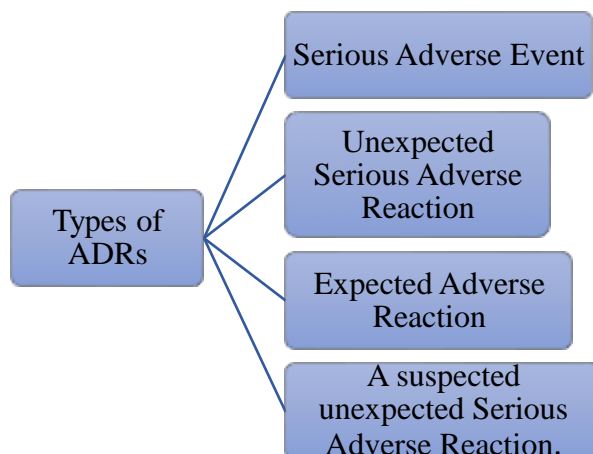
Adverse drug reactions (ADRs): An adverse drug reaction (ADRs) can be defined as unintended and noxious responses to a health product which causes at the doses usually used or tested for the diagnosis, prevention or treatment of a disease or the alteration of an organic function n drug, this scale fails to identify the offending agent.

ADR INCLUDES:

- 1) ADRs associated with newly marketed medications
- 2) Serious, life-threatening, or fatal reactions.
- 3) According to the Food and Drug Administration, a serious adverse event is one in which the patient outcome is death, life-threatening), disability, hospitalization (initial or prolonged), a congenital anomaly, or necessitates medical or surgical intervention to prevent permanent impairment or damage.
- 4) Unusual increases in numbers or severity of reactions.
- 5) Allergic reactions and idiosyncratic reactions are also considered ADRs, if they are deemed to be serious, life threatening, or fatal.

However, the definition of ADR does not include:

- a. Adverse effects of the drug which are related to the size of the dose, expected, well-known reactions and do not result in changing the care of the patient.
- b. Drug withdrawal, drug-abuse syndromes, accidental poisoning, and drug-overdose complications (e.g., drowsiness from diphenhydramine)
- c. Reactions which are extensions of the pharmacologic effect for which the drug is given (e.g., bone marrow suppression with antineoplastic agents).
- d. Disturbances totally dependent on the pathological state (e.g., diarrhea from cancer and not from a laxative).



• **Serious Adverse Event (SAE):** An adverse drug reaction or adverse event which results in death or life threatening or which requires in-patient hospitalization or prolongation of existing hospitalization.

• **Unexpected Serious Adverse Drug Reaction:** A serious adverse drug reaction which is not identified in nature.

• **Expected Adverse Reaction:** An adverse reaction or event which may have been caused by the drug or research intervention.

• **A Suspected Unexpected Serious Adverse Reaction (SUSAR):** An adverse reaction that is both serious and unexpected.

Classification of adverse reactions:

- Type A: Augmented pharmacologic effects
- Type B: Bizarre / Idiosyncratic effects
- Type C: Chronic effects
- Type D: Delayed effects
- Type E: End-of-treatment effects

The following categorization is often used:

- Type a (augmented) reaction these are based on pharmacological properties of the drug. They are more common dose related and mostly preventable and reversible. Eg. anaphylactic reaction
- Type B (Bizarre) reactions are effects that are not pharmacologically predictable but it includes hypersensitivity reactions. E.g. anaphylaxis with betalactam antibiotics.
- Type C (continuing) reactions that persist for a relatively long time. E.g. osteonecrosis of the jaw with bisphosphonates.
- Type D (delayed) reactions, these are the reactions which have become apparent after some time or after the use of a medicine. E.g. leucopenia, which can occur up to 6 weeks after a dose of lomustine.
- Type E (end of use) reactions, these are associated with the withdrawal of a medicine. E.g. insomnia, anxiety and perceptual disturbances following withdrawal of benzodiazepines.
- Type F: Failure of therapy Adverse drug reactions can be categorized in a number of ways.

MECHANISMS OF ADRS

Abnormal pharmacokinetic mechanisms due to

- Genetic factors
- Abnormal drug metabolism may be due to inherited factors of either Phase I oxidation or Phase II conjugation
- Phase I: inheriting abnormal alleles of CyP450 can alter drug metabolism; inheriting abnormal pseudo cholinesterase may affect metabolism of drugs like succinylcholine
- Phase II: inheriting abnormal N-acetyltransferase which conjugated some drugs to facilitate excretion may affect the metabolism of INH, hydralazine, and procainamide

- Comorbid disease states : Various diseases especially those that cause renal or hepatic insufficiency may alter drug metabolism. • Counterfeit drugs

Pharmacodynamic mechanisms due to synergistic effects between

- A drug and a comorbid disease state
- 2 drugs given simultaneously
- Counterfeit drugs

Advice about reporting: Report adverse experiences with medications:

1. Report serious adverse reaction: Reaction is serious when patient outcome is – Death, life threatening, hospitalization, required intervention to prevent permanent impairment or damage

2. Who can report: Any health care professional (doctors including dentists, nurses, and pharmacists) Where to report: please return the completed form to the nearest Adverse Drug Reaction Monitoring Center or to National Coordinating center.

3. What happens to the submitted information: information provided in this form is handled in strict confidence. The causality assessment is carried out at ADR monitoring centers by using WHO –UMC scale .the analyses form forwarded to national centers through ADR database.

4. The report are periodically review by national coordinating centers. The information generated on the basis of this report helps in continuous assessment of the benefit risk ratio of medicines.

5. The information is submitted to steering committee of PvPI constituted by the Ministry of Health and Family Welfare.

Avenues for patients reporting

The World Health Organization (WHO) stated that reporting routes should be made readily accessible and cheap. Patients/ consumers may submit their reports by telephone, or through fax, e-mail, e-forms and paper forms which can be submitted in a pre-paid post. Paper forms should be available at local pharmacies, healthcare facilities or offices or in magazines produced by patients, organizations.

CONCLUSION

Pharmacovigilance is essential for protecting public health by preventing, detecting, and assessing adverse reactions to medicinal products for human use. It covers the entire life cycle management of medicinal products, focusing on safety. With the increasing list of medicines, each carrying an inevitable risk of unpredictable potential harm, it plays a crucial role in addressing these threats. Reporting and analyzing adverse effects and toxicity is mandatory to communicate their significance effectively. This helps in reducing harm by ensuring the rational use of medicinal products with good quality, safety, and efficacy, considering patient expectations and concerns. To build trust among patients, predicting, managing, and communicating risks in drug use to regulatory authorities and healthcare professionals is essential.

Pharmacovigilance is complex, and errors are repeated without proper training and experience. It is crucial for systematically identifying and correlating drugs and side-effects and taking corrective actions, especially for new product launches. The importance of pharmacovigilance is evident as clinical trials have limitations in detecting rare adverse drug reactions (ADRs). If healthcare professionals consider ADR reporting an ethical obligation, the world can become safer. Emphasis should be placed on reporting serious unlabelled ADRs. Efforts to strengthen pharmacovigilance are ongoing, and it is our responsibility to ensure its effective functioning. ADR reporting should be viewed as a crucial duty rather than an additional clinical burden, ensuring safer drug use worldwide.

ACKNOWLEDGEMENT

I would like to express my deepest gratitude to my advisor (Mr. Mohammed Fareedullah) for his guidance and support throughout the preparation of this review article on “FROM ENSURING PATIENT SAFETY TO ADVERSE EVENT REPORTING AND RISK MANAGEMENT: A COMPREHENSIVE REVIEW ON PHARMACOVIGILANCE” his expertise and insightful feedback were invaluable in shaping this work. I am also thankful to my professors at (MESCO COLLEGE OF PHARMACY) for their encouragement and constructive discussions. This achievement would not have been possible without the contributions of all mentioned.

REFERENCES

1. The Importance of Pharmacovigilance, Safety Monitoring of Medicinal Products. WHO 2002, the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring.
2. Phillips KA, Veenstra DL, Oren E, Potential role of pharmacogenomics in reducing adverse drug reactions: A systematic review, JAMA, 2001, 4:2270-2279.

3. Goldstein DB, Pharmacogenetics in the laboratory and the clinic, *N Engl J Med*, 2003, 6:553-556 6.WHO [1995] safety monitoring of medicinal products; guidelines for good clinical practice [GCP], for trails on pharmaceutical products, Geneva.
4. World health organization safety of medicine: Guide to detecting a reporting adverse drug reaction. World Health Organization. Geneva 2002.
5. Pir Mohamed –M, BreckenridgeAM, Kitteringham NR, et.al adverse drug reactions. *BMJ* 1998;316(7140):1295-8. Reference adverse drug events.
6. U.S. FDA, Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, Rockville, MD, March 2005
7. Pharmacovigilance process diagram: Basic of pharmacovigilance. Brain L. Storm, “Pharmacoepidemiology” WILEY, 3rd edition, 22- 25.
8. Phase of pharmacovigilance. Pharmacovigilance: Ensuring the Safe Use of Medicines - WHO Policy Perspectives on Medicines, No. 009, October 2004. apps.who.int Bhat P, Velingkar VS, Drug Discovery- a General Overview, *Indian journal pharm education*,37(2),2003,94-99.
9. Ted Agres: FDA: New tools cut a critical path, *Drug Discovery and Development*,2004, Available at WHO, Pharmacovigilance: ensuring the safe use of medicines, Geneva: WHO 2004
10. World health organization collaborating centre for international drug monitoring (2007). The importance of pharmacovigilance available at http://www.who_umc.org cited 18 December 2007.
11. Bord CA, Rachi CL; Adverse Drug Reactions in United States Hospitals. *Pharmacotherapy*, 2006; 26(5): 601-08.
12. Hall et al. 1995; Horbuckle et al. 1999; Tuntti and Neuroren 2002. 10. Moore N (2001). The role of clinical pharmacologist in management of ADRs. *Drug safety*, 211(1): 1-7.
13. The importance of pharmacovigilance; safety monitoring of medical products, Geneva, WHO, 2002.
14. J.P Loannidis, J Lau. Completeness of safety reporting in randomized trials: an evaluation of seven medical areas. *JAMA*, 2001; 285(4): 437-443.
15. Ronald M, Elizabeth BA. 15. Moore N. The role of clinical pharmacologist in the management of ADRs. *Drug safety*, 2001; 24(1): 1-7. 27. Hall M, Mc Cormack P, Author N, Feely J. The spontaneous reporting of ADRs by nurses. *British journal of clinical pharmacology*, 1995; 40: 173-175.
16. Smith MY, Benattia I. The Patient’s Voice in Pharmacovigilance: Pragmatic Approaches to Building a Patient-Centric Drug Safety Organization. *Drug Safety* . 2016; 39(9): 779-785.
17. World Health Organization. Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action [Internet]. 2002 [cited 2015 Jun 3]. Available from: <http://apps.who.int/medicinedocs/en/d/Jh2992e/3.html>