Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

ADR Monitoring Practices in Pharmacovigilance

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ARTICLE HISTORY

Received: 12.05.2021

Accepted: 22.05.2021

Available online: 30.06.2021

DOI:

10.5530/ajphs.2021.11.11

Keywords:

Pharmacovigilance, Drug safety

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ABSTRACT

Pharmacovigilance (PV or PhV) is known as drug safety and is all about identifying, detecting, assessing, monitoring, and avoiding drug side effects. Pharmacovigilance is focused on identifying potential risks connected with pharmaceutical products and decreasing the risk of patient harm. The present review has been done to understand the advances in the pharmacovigilance programme globally and to be aware of the limitations in this area in India so that efforts can be made to overcome them and ensure greater levels of patient safety. Although India has a formal system for reporting, recording, and analyzing adverse drug responses in order to assist regulators in making future decisions about the use of dubious pharmaceuticals, the country currently lacks a reliable and complete pharmacovigilance system. To address this shortage, all stakeholders including clinical pharmacists, healthcare administrators, drug regulatory authorities, pharmaceutical companies, healthcare professionals , academic institutions, government, media representatives, health insurance companies, and patients must work together in coordination and collaboration. Only a concerted and honest effort in this area will ensure that India achieves the highest degree of patient safety.

INTRODUCTION

Pharmacovigilance, or drug safety, is the study of adverse effects that occur when drugs are used. The term "pharmacovigilance" comes from the Greek words pharmakon, which means "medicine," and vigilare, means "to keep a watch." Pharmacovigilance is primarily concerned with adverse drug reactions.[1]

Common Standard terms and Terminologies in Pharmacovigilance

Adverse Event (AE): Any external medical incident that occurs during therapy with a medical product, whether or not it has a causative relationship with the treatment.

Adverse Drug Reaction (ADR): An adverse event in which a plausible causative association between the pharmacological therapy and the noxious unwanted medical consequence is suspected. An adverse medication reaction is regarded as a probable therapy response. This possibility of a causal interaction is implied by the word "response."

Annual Report on Safety (ASR): An ASR includes a comprehensive analysis of all trials using the same Investigational Medicinal Product (IMP).

Periodic Safety Updates Reports (PSUR): This report (in an internationally agreed format) provides a periodic complete assessment of a marketed medication or biological products worldwide safety, efficacy, and effectiveness data. It includes a summary of pertinent facts, a scientific assessment, and information on sales volume, prescriptions, and population exposure.

Case studies: Case studies are individual accounts of the experiences of single patients or groups of patients. An individual patient's probable adverse reaction to a pharmaceutical product must be reported.

Evaluation of causation: According to recognized algorithms, a method for attributing probability to the likelihood of a causal association between an AE and a suspected substance.

Critical Terms: WHO Adverse Reactions Terminology

(WHOART) dictionary says "Critical Terms" may denote significant illness conditions that require special treatment.

Expected adverse reactions: Expected ADR according to reference safety information (investigator's brochure for an experimental product, overview of product characteristics) for an approved product.

ADR Frequency: ADR frequency categories are as follows.

More than 10% - very common, [1%, 10%] - common, [0.1%, 1%] - uncommon [0.01%, 0.1 percent] - rare occurrence and 0.01% - extremely rare.

Good Pharmacovigilance Practice: Pharmacovigilance is a term that refers to the monitoring of pharmaceuticals. In response to recommendations from the European Medicines Agency (EMA), the European Commission has published pharmacovigilance guidelines for human medicines in the EU.

Important medical event (IME): MedDRA provides a term list of important medical events (accessible on the EMA website) to help classify suspected ADRs, analyses data, and assess Individual Case Safety Reports (ICSR).

Risk: The probability of a particular outcome occurring (refers normally but not always to a negative outcome). Measuring the likelihood of future incidents can be referred to as risk management.

Risk management: The rate of new cases of an outcome occurring per number of people who are known to be at risk or exposed is called as risk measurement. The set of risk management activities and interventions is called the risk management System. Risk management is a three-stage process that tries to ensure that the advantages of a pharmaceutical product outweigh the dangers by the greatest possible margin by increasing the benefits or minimizing the hazards. [2]

Risk management plan (RMP): MAHs must prepare a risk management plan to implement the risk management system.

Medication error: A medication error is referred to as any mistake in the manner a drug is administered (prescription, storage, distribution, preparation, administration, and so on) that has the potential to damage the patient.

Different scales used in ADR Monitoring

Though there are several methods and tools to monitor ADR, some of the commonly used ones are discussed below.

Causality Assessment Tools

1. **Naranjo ADR Probability Scale** [Table 1]

>9 = definite ADR; 58 = probable ADR; 14 = possible ADR; 0 = doubtful ADR

2. **ADR Severity Assessment - The Hartwig Scale**

According to the severity of ADRs, Hartwig et al classified them into seven stages.

Levels 1 and 2 are considered *mild*, levels 3 and 4 are considered *moderate*, and levels 5, 6, and 7 are considered *severe*.

3. **ADR severity rating scale (Modified Hartwig and Siegel)**

Mild Level 1: The ADR does not need a change in the suspected drug's treatment. OR

Level 2: The Alzheimer's Disease

Moderate Level 3: The suspected drug must be withheld, terminated, or otherwise modified, and/or an antidote or alternative treatment must be provided. The length of stay does not change. OR **Level 4 (a):** Any level 3 ADR that adds at least one day to the length of stay. OR **Level 4 (b):** Admission is based on the ADR. Severe **Level 5:** Any level 4 ADR that necessitates immediate medical attention. OR **Level 6:** The ADR causes the patient to suffer injury. OR **Level 7:** The ADR causes the patient's mortality, either directly or indirectly.

Assessment Methods for Causality

Many researchers devised different approaches for determining causation based on various parameters including the link between the administration of a drug and the incidence of an adverse reaction, Drug and non-drug-related causes are screened, In vivo and in vitro tests to confirm the reaction, Previous experience with comparable events etc. However, there is no commonly acknowledged approach for determining causality.

Global Introspection/ expert Judgment

Individual assessments based on prior knowledge and experience in the field with no standardization technique are used to arrive at causality findings. ADR is assessed by a single expert evaluator or a group of expert evaluators.

Expert opinion or global introspection are two ways that can be used.

(i) **Swedish technique by Wilhelm et al**

(ii) **WHO causality assessment criteria for Uppsala Monitoring Centre (UMC) :** The system is used to detect medication reactions that were not expected or desired. Based on the following four criteria, the evaluation is completed. [Table2]

a) Relationships between drug use and adverse events in terms of time.

b) There aren't any other competing reasons (medications, disease process itself).

c) Drug withdrawal or dosage reduction response (de-challenge).

d) Drug re-administration response (re-challenge).

The level of causal link is divided into four levels based on the fulfilment of a number of the criteria listed above.

i. Certain Good time, no other explanation, plausible withdrawal reaction, "definitive" re challenge

ii. Probable good timing, improbable other cause, withdrawal

iii. Possible - Appropriate time, as well as other factors.

vi. Unlikely - Inadequate timing, other factors are more likely.

Following examples explain this.

1.Certain: Dizziness caused 34 hours after of taking an oral antihypertensive medicine with no other medications. AE stops when the drug is stopped (positive DE- challenge) and resumes when the drug is taken again (positive re challenge).

30 seconds after a subcutaneous injection, a reaction at the

Table 1 : Naranjo ADR Probability Scale

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

definite	if the overall score is 9 or greater
probable	for a score of 5-8
possible	for 1-4
doubtful	if the score is 0

(Courtesy Reference: A method for estimating the probability of adverse drug reactions. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. Clin Pharmacol Ther. 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154. PMID: 7249508)

injection site. When ingesting a large tablet, it becomes caught in the pharynx (obstruction) and must be removed in the emergency room.

2. Probable: Thrombocytopenia as a result of an oncology medication. Ampicillin-induced diarrhea, after taking an antibiotic for bronchitis, development of vaginal candidiasis.

3. Possibly: Impaired liver function tests as a result of antihistamine use.

4.Unlikely: Colon cancer discovered after three course antibiotic treatments. Myocardial infarction three weeks after taking a medication with a 10-minute terminal half-life.

Case Report: A 68-year-old woman given 30 mg Pamidronate to treat osteoporosis

ADR developed - Arthrosis, exacerbated Arthritis.

Result: The patient was not able to be rehabilitated. Negative DE challenge

Drug-related evaluations

1. Method of Probabilistic / Logistic Analysis

Methods based on probabilities (Bayesian approaches) -The Bayesian techniques are a flexible way to convert an earlier estimate of the probability of a drug being the cause of an illness into a posterior estimate of the likelihood of that drug causing the illness. Epidemiological data is used to calculate the prior probability, while evidence from each case is used to calculate the posterior probability. [3]

Table 2 : WHO-UMC Scale

Causality Item	Assessment criteria (all points must be reasonably complied)
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake. • Cannot be explained by disease or other drugs. • Response to withdraw plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective of medical disorder or a recognized pharmacologic phenomenon) • Rechallenge satisfactory, if necessary.
Probable/Likely	• Event or laboratory test abnormality with reasonable time relationship to drug intake. • Unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable. • Rechallenge not required.
Possible	• Event or laboratory test abnormality with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs.
Unlikely	• Information on drug withdrawal may be lacking or unclear. • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation.
Conditional/Unclassified	• Event or laboratory test abnormality. • More data for proper assessment needed, or • Additional data under examination.
Un assessable/Unclassifiable	• Report suggesting an Adverse Drug Reaction. • Cannot be judged because information is insufficient or contradictory. • Data cannot be supplemented or verified.

2. Algorithms

It comprises of a problem-specific flow chart with step-by-step instructions for arriving at a solution. In fact, its form includes a questionnaire, the responses to which reveal the etiology of a certain ADR. In a systematic manner, it provides structured and standardised techniques of assessment. ADRs are evaluated using parameters such as the time it takes for an ADR to appear or the temporal sequence of events, previous drug/adverse reaction history, and so on.

Methods and types of algorithms

There are various computational approaches for determining causality, however no single algorithm is acknowledged as the "gold standard" due to several flaws. The following are some of the most important algorithmic methods:

a. The French method of Dangaumou, the method of Kramer et al., Using the Naranjo scale, Method of balanced assessment, summary time plot and Drug Interaction Probability Scale (DIPS) - Ciba Geigy approach.

b. Applying Naranjo scale is a frequently used technique. The method used to determine the chance that an ADR is caused by the drug and not by other factors. It consists of ten questions to which you can respond with "yes," "no," or "unknown" (don't know). These responses are graded on a scale of Definite, Probable, Possible, and Doubtful.

When the overall score is 9 or greater, it is considered definitive, when a total score of 58 is obtained, it is considered probable, when you get a total score of 14, it's possible, When the overall score is less than 0, it is considered doubtful. [4]

Research on Adverse Drug Events and Reports (RADAR)

The RADAR project is a pharmacovigilance programme that specializes in identifying, evaluating, and distributing information about major adverse drug reactions (ADRs) (those that lead to death or serious organ dysfunction) as well as therapeutic interventions. The Department of Veterans Affairs, the American Cancer Society, the National Cancer Institute, and the National Heart, Lung, and Blood Institute have all been involved in the RADAR project. Even though the pharmaceutical manufacturers have been asked to provide clinical information on each major ADR, they fail to help. The project manager of the RADAR project, and its 25 investigators are made up of various fields of medicine, clinical pharmacology, epidemiology, statistics, and pharmacy. A serious ADR may occur during a clinical observation or clinical reporting. When this occurs, an investigation is launched. The World Health Organization (WHO) utilizes WHO criteria to assess whether there is a cause-and-effect link between the suspicious drug and the occurrence.

The researchers on ADRs from RADAR looked at 16 major ADRs. The RADAR investigators' proactive safety efforts are more comprehensive than those of the Food and Drug administration (FDA) and pharmaceutical makers, but the dissemination of associated safety notifications is slower. Adverse drug reactions (ADRs) account for $3.6 billion in yearly health-care costs and are one of the top ten main causes of death.

There is a need for new ways to detecting unanticipated pharmacological harmful effects.

One source of concern is that present pharmacovigilance efforts are hampered by low reporting rates, and the information provided when ADRs are reported is of varying quality. Safety notices are handed out when pharmaceutical companies and the FDA are certain that an incident constitutes a significant ADR. If the distribution of these messages is delayed, the safety notification is incomplete, or the physicians do not read the notices, major ADRs may go unnoticed.

Monitoring Methods Examples

Surveillance in the Passive Mode

1. Automatic reporting- A working ADR system to keep track of the safety of all drugs. The information is gathered and stored in a central or regional database.

2. Reporting that is stimulated: An increase in reported adverse events as a result of a government alert about a drug or an individual AE is known as "stimulated reporting."

3. Intensified reporting - This is an extension of the programme of spontaneous reporting. Its goal is to improve early post-marketing ADR reporting for certain drugs.

4. Targeted spontaneous reporting - This strategy is utilized to learn more about a medicine's ADR profile in the general population.

Pharmacovigilance Quality System

Pharmaceutical Quality Management System (QMS) are the policies, procedures, and systems that ensure that activities related to detecting, assessing, understanding, and evaluating potential side effects or any other medication-related issue are performed in accordance with applicable laws, regulations, and company policies. To realize the highest ethical standards, QMSs must enforce legal and contractual requirements that are as well as customer/licensing partner requirements. In order to produce high quality products and services, businesses must develop a quality policy as well as an approved written library of Standard Operating Procedures (SOP), quality control procedures, key performance indicators (KPIs), job descriptions, and training programmes.

If processes deviate, and those deviations point to a quality concern, a route cause analysis is performed, and then an action plan to address the concern is developed corrective and preventative action plan (CAPA). It is essential that all the listed activities be integrated into the quality system: high standards of quality assurance and control. [5]

All of the following activities must be included in the quality system:

1. Careful planning

2.Adherence to high standards

3. Quality assurance and control

4. Enhancements in quality.

Pharmacovigilance database and signal detection

A pharmacovigilance safety database is a consolidated repository for individual case safety reports (ICSRs) received from all sources worldwide for a company's medical product(s). Any pharmacovigilance safety database must be kept up to date with the current regulatory requirements and certified to suit international standards as well as corporate needs. This is because safety databases make it easier to disclose individual and aggregate safety data to authorities and third parties, as well as providing crucial information for the identification of safety signals and continual review of a company's product's risk-benefit profile.

Pharmacovigilance is increasingly focusing on signal identification and management. Companies must be able to manage signals that are discovered, such as assessing them to determine the clinical risk in the context of many influencing factors in a convincingly controlled manner.

The process of actively searching for and recognizing safety signals from a range of data sources is known as signal detection in pharmacovigilance.

The disease that a drug, vaccination, or treatment is meant to treat, the disease's and product's distribution, clinical trial results, environmental variables, and other epidemiological factors all influence the benefit/risk balance. Signal handling necessitates a complex workflow and a high level of process control.

The most prevalent source of signals is biopharmaceutical companies' spontaneous reporting systems, which are required by regulators to be retained. These records are kept in a database that is either hosted and managed by the corporation or outsourced to a technology or full-service contract research firm (CRO). As part of periodic monitoring, signal detection on this database is required. Data from national databases such as the FDA Adverse Event Reporting System (FAERS), Surveillance, and VigiBase are also valuable sources of possible signals.

A Solution for Robust Signal Detection and Safety Data Analysis

Pharmacovigilance database contains a lot of critical product information. *PV-broad Analyzer's* data mining and reporting

capabilities put this information at your fingertips, allowing you to create detailed studies and graphical outputs for internal and external usage. The data sets can also be subjected to common mathematical functions such as count, sum, average, max/min, and standard deviation. To maximiser flexibility in creating such essential metrics, the application connects easily with PV-Works, other PV software, and numerous external data sources.

Assessment and management of pharmaceutical risks

Risk management is used in pharmacovigilance to ensure that medicines are used safely and that patients' health is protected. It is a series of activities that are carried out to identify risk, assess risk, and minimize and prevent risk. Risk management's overall goal is to ensure that the pharmaceutical product's advantages outweigh the dangers by a large margin for the treatment of a certain indication, both at the individual level and for the target population as a whole. The WHO's Uppsala Monitoring Centre (UMC) is the operational hub for the WHO's International Drug Monitoring Program, which today includes a network of national pharmacovigilance centers in about 150 countries, covering 95% of the world's population. Risk management includes identifying and characterizing the medicinal product's safety profile, designing pharmacovigilance activities to study the drug's risks, developing methods to limit risk, and assessing their success. The risk management strategy is formed from each of these efforts, and must be presented during the medication approval process.

Developing a risk management plans (RMPs)

RMP is a document that provides an in-depth look at the knowledge currently known about a pharmaceutical product's safety and efficacy. The RMP contains critical information on study designs and other activities that will help researchers learn more about the medicine's safety and efficacy. It also outlines the steps that must be followed to avoid or reduce the dangers connected with the product's use in patients. For any new medicinal product for human use, marketing authorization holders must have an RMP, which must be presented at the time of marketing authorization application. RMPs for nationally licensed items must be reviewed and approved by the Health Product Regulatory Authority, HPRA.

Writing a case narrative

The most critical aspect of establishing a drug's safety profile is to evaluate every adverse event (AE) that a clinical trial participant experience. Any investigator or sponsor can offer this information through narratives created following the investigation of a significant adverse event.

Every stakeholder, health-care professionals, patients, regulators, Ethics Committees, policymakers, and the health ministry must have access to high-quality, up-to-date information about medicines and their use, as well as health care in general, and ways to promote health and avoid any adverse effects, tailored to their abilities and preferences. The most crucial feature is that doctors, nurses, pharmacists, and patients all understand that documenting patients' experiences with drugs, particularly unpleasant effects, will assist to improve therapy and safeguard future patients. [6]

Serious Adverse Event (SAE) narrative is a complete, stand-alone document that offers a full and clinically relevant, sequential account of the evolution of an incident or events, according to the International Conference on Harmonisation (ICH). The specifications include information related to the patient (such as characteristics, history, and symptoms), the therapy (what was done and why), medical history (including what occurred during the medical course of the event), diagnosis (how it was diagnosed), and AEs (the possible side effects), as well as the result (what happened and what was found), as well as any other relevant information (such as laboratory evidence) or evidence (such as lab ranges).

Pharmacovigilance perspectives in India

India is a vast country with a pharmaceutical industry valued at $18 billion and exporting nearly 40% of generic medicines worldwide. It should be made mandatory, and regulatory organizations should conduct regular inspections to ensure that pharmaceutical businesses have an effective pharmacovigilance system. Though Indian pharmacovigilance data is collected through Pharmacovigilance Programme of India (PvPI), it is only shared with WHO by vigiflow. Vigiflow is a web-based system used by WHO-based Pharmacovigilance Centers to manage individual case safety reports (ICSRs). There is no effective official system in place to ensure that data received by PvPI is shared as effectively and as early as possible with the concerned pharmaceutical companies and health care professionals, allowing companies and prescribers direct access to ADR data for understanding and managing the risks associated with the use of specific drugs. Though the number of ADRs reported by healthcare professionals has increased, the veracity of the ADRs reported remains in issue. There is currently no system in place to limit the reporting of bogus data. A counter-check method is required so that pharmacovigilance can be depended upon blindly for future drug restrictions. The recent prohibition of several high-profile drug withdrawals has prompted regulatory authorities to raise the bar. Another issue in the Indian system is the lack of pharmacovigilance infrastructure, resources, and facilities. The World Bank is now sponsoring India's National Pharmacovigilance Program; however, the Health Ministry's budget does not include any funds. To give the programme a robust foundation, the government's contribution in terms of financial, technical, and manpower aid is unquestionably required. Politicians at all levels, national, regional, and local, can help achieve this. There are extremely few people who are appropriately trained to handle all aspects of pharmacovigilance

The Pharmacist's role in ADR monitoring

A pharmacist works as an ADR reporter. As part of their professional activity, pharmacists are responsible for monitoring the continuous safety of drugs. A medicine must be viewed as a notion with a benefit-risk profile that can be used to treat patients using proven or widely agreed-upon methods where the benefits outweigh the dangers. Pharmacovigilance refers to the role of pharmacists in a worldwide context. The collecting of adverse drug reaction (ADR) reports from various stakeholders responsible for monitoring the medicine's safety profile is referred to as pharmacovigilance.

The term "relative absence of harm" can be used to describe safety. In pharmacovigilance, safety refers to the gathering of reports of drug side effects. The term "safety" can refer to gathering information and coming up with a solution to determine whether or not a drug should be used again. A pharmacist should also be involved in the collecting of data for longitudinal pharmacoepidemiologic research. Pharmacists play a critical role in the management and prevention of drug-related adverse effects. When medications are approved or authorized, safety issues are frequently assumed. The scope has now been expanded.

It encompasses all safety-related activities beginning with the first human exposure to a new medicine. It should be mentioned that pharmacists have the added benefit of being able to interact directly with patients. Because the most serious adverse drug events occur in hospitals, hospital pharmacists can play an important role in ADR reporting. [7]

Because pharmacists are present at all levels of medical treatment, from community pharmacies to primary healthcare centers, government hospitals to corporate hospitals, they may be trusted as an effective instrument in the collection and reporting of ADRs. Clinical pharmacy includes not only drug-drug and drug-food interactions, but also recording adverse drug effects, decreasing medication errors, and monitoring patients' health.

CONCLUSION

To summarize, India has long been interested in pharmacovigilance, but the programme has not been as successful as in the Western world. Although India has a formal system for reporting, recording, and analysing adverse drug reactions to assist regulators in making judgments about the use of dubious pharmaceuticals in the future, the country currently lacks a solid and comprehensive pharmacovigilance system. A successful pharmacovigilance programme is not run by a single person. To overcome the shortage, all stakeholders, including healthcare administrators, drug regulatory authorities, pharmaceutical companies, healthcare professionals (physicians, dentists, pharmacists, nurses, and others), academic institutions, government, media representatives, health insurance companies, and patients, must work together in coordination and collaboration. Only a concerted and honest effort in this area can ensure India's attainment of the greatest level of patient safety.

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Cite this article : Jeny Samuel, Aiswarya Prasad, Boby Johns G.
ADR Monitoring Practices in Pharmacovigilance
Asian J. Pharm. Hea. Sci.. 2021;11(2):2482-2488. DOI : 10.5530/ajphs.2021.11.11