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An Approach to Study Pharmacovigilance

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ABSTRACT

Pharmacovigilance is started in the clinical stage and is continued throughout the entire drug's life cycle. It is defined as the study, identification, and prevention of potential drug-related issues and side effects, with emphasis being placed on the acute and long-term impacts of pharmaceuticals, biological products, herbal remedies, and traditional treatments. Recently, pharmacovigilance has been changed, and its role is being considered increasingly crucial in improved clinical practice and public health research. A range of techniques is employed in pharmacovigilance, including focused clinical investigations, stimulated reporting, passive and active surveillance, comparative observational studies, and descriptive research. New advances in pharmacovigilance are considered crucial for meeting patient needs and for ensuring that their health is maintained. Additionally, it is suggested that pharmacovigilance techniques be used to determine which patients are susceptible to adverse drug reactions (ADRs) and in what ways such reactions might occur. For this process, the use of patients as information sources is considered crucial in the pharmacovigilance sector.

Keywords: *Pharmacovigilance, Drug Safety, Clinical Trials, Adverse Drug Reaction*

INTRODUCTION:

Pharmacovigilance is considered an important and integral part of clinical research [1]. Both clinical trial safety and post-marketing pharmacovigilance are regarded as critical throughout the product lifecycle. Pharmacovigilance is defined as the pharmacological science related to the detection, assessment, understanding, and prevention of adverse effects, particularly the long-term and short-term adverse effects of medicines [2]. In India, pharmacovigilance is still regarded as being in its infancy, and very limited knowledge about the discipline is possessed. While major advancements in the discipline of pharmacovigilance have been achieved in Western countries, not much has been accomplished in India [3]. An immense need is felt for the importance of pharmacovigilance to be understood and for its impact on the life cycle of the product to be realized. Through this understanding, the integration of good pharmacovigilance practices in processes and procedures can be enabled so that regulatory compliance may be ensured and clinical trial safety and post-marketing surveillance may be enhanced [4]. Pharmacovigilance is not new to India and has infact been going on from 1998 [5]. Further India is becoming a hub for clinical research activities due to its large population, high enrolment rate and low cost [6]. Drug safety and pharmacovigilance are regarded as dynamic clinical and scientific disciplines. Pharmacovigilance has been defined by the World Health Organization (WHO) as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [7]. A vital role is played by it in ensuring that sufficient information is provided to doctors and patients for making decisions regarding the choice of a drug for treatment [8]. However, despite all their benefits, evidence continues to be obtained that major adverse reactions to medicines constitute a common, yet often preventable, cause of illness, disability, and even death. In some countries, adverse drug reactions (ADRs) are ranked among the top 10 leading causes of mortality. In order to prevent or reduce harm to patients and thus improve public health, mechanisms for the evaluation and monitoring of the safety of medicines in clinical use are considered vital [9]. The potential implications of pharmacovigilance programs in the next 10 years on the evolution of the science are expected to be significant. These days, many challenges are being faced by pharmacovigilance in the development of better health care systems on the global stage. Major challenges are posed by globalization, web-based sales and information, broader safety concerns, the balance between public health and pharmaceutical industry economic growth, the monitoring of established products, issues in developing and emerging countries, attitudes and perceptions toward benefit and harm, and the measurement of outcomes and impact [10].

AIMS OF PHARMACOVIGILANCE

Improve patient care and safety in relation to the use of medicines and all medical and Para medical interventions [11].

a) Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
b) Pharmacovigilance keeps track of any drastic effects of drugs.
c) Improve public health and safety in relation to the use of medicines.
d) Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
e) Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public [12].
f) For many years, the effectiveness of pharmaceuticals has been studied and their side effects have been monitored, starting in the laboratory and continuing through the pharmacy [13].
g) Safety and patient care with regard to medication use and any additional medical and paramedical procedures are enhanced [14].
h) Any severe side effects of medications are monitored through pharmacovigilance.
i) The safe, rational, and more effective (particularly cost-efficient) use of medicines is encouraged by ensuring that the benefits, harms, effectiveness, and risks associated with their use are examined [16].
j) Public safety and health in respect to drug consumption are strengthened [17].

History

The history of pharmacovigilance was stated to date back around 170 years, even though it was not yet known by that name at the time. It was explained that pharmacovigilance had been considered a planned activity in the field of professional health care with significant social and economic ramifications, aimed at evaluating drug risk/benefit ratios, enhancing patient safety, and improving quality of life. The accomplishments of pharmacovigilance were outlined in that context. It was further mentioned that, in order to comprehend the steps marking its historical evolution, reference had to be made to the earliest reports, which were said to have been in the form of letters or cautions issued by physicians to publishers of significant and well-known scientific journals, compared with the highly structured computerized registers of the present day. It was pointed out that these historical periods also helped in understanding why pharmacovigilance had enabled significant improvements in human health and in Materia medica itself, while also allowing the recognition of obstacles expected in the upcoming years [18].

Pharmacovigilance Programme of India (PvPI)

The Pharmacovigilance Programme of India (PvPI) is an Indian government organization which identifies and responds to drug safety problems.[1] Its activities include receiving reports of adverse drug events and taking necessary action to remedy problems [19]. The Central Drugs Standard Control Organisation established the program in July 2010 with All India Institute of Medical Sciences, New Delhi as the National Coordination Centre, which later shifted to Indian Pharmacopoeia Commission in Ghaziabad on 15 April 2011 [20].

Table 1: The chronological pharmacovigilance evolution with particular reference to India [21-25].

Year	Evolution
1747	First clinical trial by James Lind to prove the effect of lemon juice in treatment of scurvy
1937	Demise of 100+ infants due to sulphanilamide toxicity
1950	Reported aplastic anemia due to chloramphenicol toxicity
1961	Global catastrophe by thalidomide toxicity
1963	Recollection of immediate action on ADRs by World Health
1968	WHO researches for global drug monitoring on pilot scale.
1996	International standard level clinical trials introduced in India
1997	India merged with WHO ADR monitoring program
1998	Commencement of pharmacovigilance in India
2002	67th National Pharmacovigilance Centre was vested in India
2004-2005	National Pharmacovigilance Program was established in India
2009-2010	PvPI (Pharmacovigilance Program) was commenced
2012	Haemovigilance was started
2015	Commencement of MvPI (Materiovigilance)

Worldwide soldiers

There exists a quite complex and exquisite relationship between extensive fields of companion in the practice of drug safety monitoring. These companions essentially anticipate, acknowledge and respond to the frequently increasing demands and expectation of the people, health care professionals, and policy official

Table 2: Role of Different Departments in The Pharmacovigilance Study [26-34].

Department	Purpose
The Quality Assurance and Safety	The Department of Essential Drugs and Medicine Policy within WHO and pharmaceutical companies are regarded as being part of this effort. The gap between the potential offered by the drug and the reality of its usage by the worldwide population is closed by them.
The Uppsala Monitoring Centre	The global database of ADR reports received from national centres is managed by it. Communication among countries to provide rapid identification of signals has been accomplished by them.
The National Pharmacovigilance Centre	Public awareness of drug safety is increased. Active surveillance programs have been established by vital centres in developed countries through the use of record linkage and PEM, and epidemiological reports on ADRs for specific drugs have been collected.
Hospitals and Academic	Many medical institutes have developed ADR and medication fault close watch system in their premises. Academic centres provide an important role in pharmacology by teaching, clinical research, training, ethics program and clinical service
Health Professional	A lot of healthcare professionals from different categories will observe different kind of drug problem

Need for Pharmacovigilance

Pharmacovigilance is regarded as a salient and constitutive part of clinical research. Despite its 40-year history, pharmacovigilance is still considered a dynamic scientific and clinical field. An important role continues to be played in meeting the challenges posed by the increasing range and potency of drugs. When adverse events and toxicity occur, especially when not previously known, it is regarded as essential that they be reported, analysed, and their significance effectively communicated to the subject with knowledge. The knowledge required to interpret the information, which is considered inevitable and certain for all drugs, is viewed as having a trade-off between potential benefits and harms [35]. Suffering can be minimized by ensuring that good quality, safe, and effective medicines are appropriately used and that patient expectations and concerns are taken into account when treatment decisions are made. The consumption and prescription of medicines are recognized as among the most common activities of patients and their caregivers. It is therefore regarded as logical that those medications be subjected to the same rigorous standards of oversight as those applied in the creation and evaluation of pharmaceuticals, and that prescribing practices and the degree of rational and cost-effective use be examined [36]. It is commonly acknowledged that the clinical development of medications is a difficult process requiring a long time for completion. Once a medication is marketed, the safe and secure scientific setting of clinical trials is left behind, and its availability for general public use is established. Currently, only a small number of carefully chosen individuals are used for testing the short-term safety and effectiveness of the majority of medications. Pharmacovigilance is therefore considered necessary, entailing the assurance of early detection of novel adverse reactions or patient subgroups with extraordinary sensitivity, and the establishment of specified methods to mitigate such risks [37]. Furthermore, it is regarded as crucial that after marketing, fresh and medically still-developing medications be examined for their efficacy and safety in actual use. Additional knowledge is generally required concerning the effectiveness and safety of long-term drug use in combination with other medicines, particularly when employed in specific populations such as children, pregnant women, and the elderly. Numerous negative effects, drug interactions, and risk factors have been documented during the years following drug release [38]. These years were also marked by the advancement of pharmacovigilance awareness, education, and clinical training, as well as effective public outreach. Additionally, processes and procedures for gathering and analyzing reports from patients were built, and information for consumers, practitioners, and regulators on the effective utilization of medications was designed [39].

Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as "an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects are usually predicted as hazards from future administration and are considered to warrant prevention, specific treatment, alteration of the dosage regimen, or withdrawal of the product" [40,41].

Table 4: Detailed classification of ADRs [33]

Type of reaction	Features	Examples	Management
A: Augmented Reactions (Dose related	Common Predictable Low mortality	Digoxin toxicity, Respiratory, depression with opioids	Reduce dose Consider concomitant therapy
B: Bizarre Reactions (Non-dose related)	Uncommon Unpredictable High Mortality	a: Immunologic Reactions b: Idiosyncratic reaction	Reduce dose Consider concomitant

			therapy.
C: Chronic Reactions (Dose and time related)	Uncommon Cumulative dose related	Osteonecrosis of the jaw with bisphosphonates	Avoid / withhold.
D: Time related Reactions (Delayed)	Uncommon Usually, dose related	Carcinogenesis Teratogenesis	Reduce dose; Withdrawal May have to increased
E: End of Use Reactions (Withdrawal)	Uncommon Soon after drug withdrawal	Withdrawal syndrome With opiates/barbiturates	Withdraw drug slowly
F: Unexpected Failure Of therapy (Failure)	Common Caused by drug interaction	Resistance to anti- microbial agents	Consider concomitant therapy

Factors Affecting the Occurrence of ADRs

For the majority of adverse events, especially idiosyncratic drug reactions, predisposition is considered to be multi-factorial and is regarded as involving environmental and genetic flaws, concurrent infections, and the use of additional medications for various illnesses. The majority of adverse drug reactions (ADRs) are believed to originate from the prolongation of a drug's intended pharmacologic effects, frequently attributed to significant individual patient variability in pharmacokinetics and pharmacodynamics. The pathophysiology of ADRs is described as involving pharmacological, immunological, and genetic components [44].

Pharmacological ADRs are considered to be predisposed by factors such as dose, drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and medication interactions. The need for many atypical pharmacological reactions has also been recognized, with the metabolic conversion of medicines to metabolites being regarded as a significant factor [45].

Some of the factors that influence ADRs are classified as follows [45–54]

A. Patient related factors

a. Age
b. Gender
c. Maternity Status
d. Foetal Development
e. Creatinine Clearance
f. Allergic Reactions
g. Body Weight and Fat Distribution

B. Social factors

a. Alcohol consumption
b. Race and ethnicity factors
c. Smoking

C. Drug related factors

a. Poly pharmacy
b. Drug dose and frequency

D. Disease related factors

Clinical Trials

To assure the safety and effectiveness of any new treatment, the process of clinical research is regarded as a crucial step in drug discovery. In the present global scientific era, clinical trials are considered essential for bringing new and improved medications to market. Human volunteers (subjects) are recruited for clinical trials so that prospective treatments can be tested to determine whether their certification for use in the general population is warranted [55]. Clinical trials are described as collections of experiments and observations performed on human participants in clinical research. They are conducted in the search for novel therapies, interventions, or diagnostic procedures in order to prevent, detect, treat, or manage various illnesses or medical disorders. Through such trials, an assessment is made of whether a novel intervention is safe, effective, and superior to currently available treatments [56]. According to the WHO, a clinical trial is defined as *"*any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." The basic goal of drug discovery research is considered to be the creation of novel, safer, and more effective medications for human use. Before release onto the market, a new medicine is required to undergo numerous stages of rigorous testing, first on animals and then on human beings [57].

Types of clinical trial [50]

1. According to the mode of study
    A. Interventional Study
    B. Clinical observational study
2. According to the purpose
    A. Prevention trials
    B. Diagnostic trials
    C. Treatment trials
    D. Supportive care trials
    E. Screening trials
    F. Compassionate use trial [50].

Phases in clinical trials [49].

Fig. 2 Phases in clinical trials.

Methods Incorporated in Pharmacovigilance

1. Spontaneous Reporting System (SRS)

Spontaneous reporting systems (SRS) were developed and have now been adopted as the main method for gathering data on the safety of medicines after they have been placed on the market. The identification of new, uncommon, and significant ADR signals as early as possible is regarded as the primary purpose of SRS. Reports of suspected ADRs can be received more frequently by a pharmacovigilance centre from physicians, pharmacists, and patients through the use of a spontaneous reporting method [34–36].

The gathering and analysis of information, as well as the alerting of stakeholders to potential risks when new ADR signals are detected, are considered the primary responsibilities of the pharmacovigilance centre [84]. The pharmaceutical industry is also served by spontaneous reporting, through which data regarding its products are obtained. All medications on the market are able to be monitored effectively and affordably throughout their full life cycle by means of an SRS [85].

Selective reporting and underreporting are regarded as the fundamental criticisms of this strategy. The determination of cause-and-effect correlations or precise incidence rates through an SRS is considered impossible. Likewise, the comprehension of risk factors or the interpretation of usage patterns cannot be achieved by this method [86].

Despite these criticisms, the value of spontaneous reporting has been established over time, even though it is often claimed by critics that it does not rep0resent the best technique for ensuring pharmaceutical safety [87].

2. Intensive Monitoring

Intensive monitoring has a non-interventional observational cohort as its foundation. Intensive monitoring delivers real-world clinical data by being non-interventional and involving neither inclusion nor selection criteria during the data collection period. Selection bias is eliminated because it is unaffected by the types of inclusion and exclusion criteria that define clinical studies. The methodology's foundation in event monitoring, which enables it to spot signals for outcomes that weren't necessarily suspected to be adverse drug reactions (ADRs) of the medicine under study, is another advantage [88].

The incidence of adverse events can also be assessed thanks to intensive monitoring programmes, allowing for the calculation of the risk of specific ADRs. However, this strategy also has known drawbacks. Unknown is the percentage of negative effects that are not disclosed to medical professionals. In addition, reported event rates rather than actual incidence rates are produced by the studies. This holds true for all research projects using computer databases and record linking that use information from medical records. Standard intensive monitoring studies lack a control group, so the actual background incidence of occurrences is unknown [89].

Pharmacovigilance Process

Processes involved:

1. Collect and record ADRs
2. Causality assessment and analysis of ADRs
3. Collate and code in database
4. Compute risk benefit and suggest regulatory actions
5. Communicate for safe use of drugs among stakeholders [76]

Signal Detection

The World Health Organization (WHO) has defined a signal as: Reported information on a possible causal relationship between an adverse event and a drug,[48] the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal[49], depending upon the seriousness of the event and the quality of the information. In actuality, the majority of signals will pertain to threats that were previously undetected, but in the middle of the 1990s [50], there was a remarkable instance of a signal that a known hazard was more serious than assumed [51]. Tiaprofenic acid, a NSAID medicine, had been known to cause cystitis for more than a decade, but a string of cases showed that, if the reaction was not recognised and the drug was continued for an extended period of time, severe chronic cystitis might happen [52]. As a result, surgical bladder excision was frequently required, which left patients permanently disabled [53]. Although some signals can be picked up passively (such from the medical literature), signal detection should generally be an intentional effort. Although there are probably many needles to discover, it has been stated that identifying signals in huge datasets is similar to trying to locate a needle in a haystack. In this regard, the phrase "data mining" is now frequently employed, especially in reference to the systematic detection of signals from huge spontaneous ADR databases. Data mining is defined as "actively seeking patterns in large datasets [54]."

National Programme For Pharmacovigilance

Clinical trials, which are limited by the number of patients and length of the trial as well as by the extremely controlled environments in which they are conducted [70], are the only way to gain experience with a product's safety and efficacy prior to its commercialization. These trials do not reflect practise conditions [71]. Once a drug is marketed, how it is utilized in the hospitals or in general practise may not exactly match the settings under which patients are examined during the pre-marketing phase [72]. It is frequently insufficient or impossible to obtain information on uncommon but severe adverse medication responses [73], chronic toxicity, use in particular populations (such as pregnant women, children, and the elderly), and drug interactions [74]. Before a very large number of patients have taken the medication, certain ADRs might not be discovered [75].

Therefore, one of the crucial post-marketing strategies for ensuring the effectiveness of pharmaceutical and associated health goods is pharmacovigilance [77, 78].

1. Evaluating the risks and benefits of medicines to ascertain what, if any, action is required to enhance their safe use [79].
2. Educating people on how to utilise medications most safely and effectively [80].
3. Following up on any action's effects [81].

A set of standard reference books is required to be made available to the centres recognized by the NPAC. These include Meyler’s Side Effects, AHFs Drug Information Handbook, Martindale, Davies Textbook of ADR, Physicians’ Desk Reference, and the British National Formulary [81].

Good Pharmacovigilance Practices

The fundamental foundation of good pharmacovigilance practise is the collection of comprehensive data from spontaneous adverse event reports, sometimes referred to as case reports. To create case series for interpretation, the reports are employed [82].

Good Reporting Practice

Signals of drug side effects may be produced by spontaneous case reports of adverse outcomes submitted to the sponsor and FDA as well as reports from other sources, such the scientific literature or clinical studies. For an accurate assessment of the connection in between product and unfavourable outcomes, the reports' quality is essential. FDA advises sponsors to use trained healthcare professionals to contact reporters and urges sponsors to make a reasonable effort to acquire full

data for case analysis at initial contacts and subsequent follow-up, particularly for serious incidents. The line of questioning can be narrowed down with the aid of computer-assisted interviewing, targeted questionnaires, or other techniques designed to focus on certain occurrences. When a consumer reports an adverse event, it is frequently crucial to get their consent before contacting the healthcare provider who is aware of the patient's adverse event in order to gather more medical data and, if necessary, collect pertinent medical records. The FDA advises that the gravity of the incident reported, the report's source (such as a healthcare provider, patient, or published source), and other considerations should determine the extent and methodology of case follow-up. The FDA advises that major adverse event reports, particularly those of adverse events not previously associated with the medicine, should receive the most rigorous follow-up attention [83].

Characteristics of a good case report:

The following components are found in effective case reports:

- **A.** A description of the disease or unpleasant effects experienced, including the timing of the development of symptoms or indicators [79].
- **B.** Details of suspected and concurrent roduct therapy, including over-the-counter drugs, dietary supplements, and recently stopped drugs (i.e., dose, batch number, routine, dates, and length) [81].
- **C.** Patient characteristics such as age, race, and sex; baseline medical state before the initiation of product therapy; co-morbid conditions; concurrent drug use; pertinent family medical history of disease; and the presence of other risk factors are required to be recorded.
- **D.** The assessment of the events, including the techniques utilized to perform such assessment, is to be documented. Patient outcomes and the clinical course of the incident (e.g., hospitalization or death) are also to be recorded.
- **E.** Appropriate blood levels and pertinent treatment measurements, including laboratory data at baseline, during therapy, and after therapy, are to be included.
- **F.** Any additional pertinent information (such as details regarding the event or data concerning the patient's benefits, if relevant to the examination of the event) is also expected to be documented. Information regarding responsiveness to dechallenge and the established goal is required to be noted.
- **G.** Sponsors are advised by the FDA to include all pertinent data from the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy in the case narrative section of a medication error report.
- **H.** Although use of the taxonomy is not mandated for sponsors, it has been discovered by the FDA to be a useful tool for the categorization and analysis of pharmaceutical error reports.
- **I.** A common vocabulary and an organizational framework for the information gathered through pharmaceutical error reports are provided by it.

Safety Signals That May Warrant Further Investigation

According to FDA, the aforementioned techniques will enable a sponsor to recognise and provisionally characterise a safety signal. Since it is impossible to characterise every event with absolute certainty and because there is almost always underreporting to a certain degree and inadequate information about the length of therapy, the number of patients treated, etc., it is impossible to estimate the actual danger to patients from these data [111,122].

1. New, unlabeled unfavourable events, particularly if they are serious [112].
2. A labelled event that appears to have become more severe [113].
3. The occurrence of serious incidents deemed to be incredibly infrequent in the general populace [114].
4. brand-new interactions between products, devices, foods, or dietary supplements [115]
5. The discovery of a community at risk that had not previously been recognised (for example, populations with different ethnic or hereditary tendency or co-morbidities) [116].
6. Uncertainty over the name, labelling, packaging, or application of a product [117].
7. Issues relating to how a product is utilised (such as adverse events observed at doses greater than those on the label or in individuals not advised for treatment) [118.121]
8. worries resulting from a risk minimization action plan's potential deficiencies (for example, reports of grave incidents that seem to indicate the failure of a RiskMAP target) 119]
9. Additional issues that the company or FDA have identified [120,123].

Pharmacovigilance Analytical Tools

It is commonly recognized that pharmacovigilance (PV) is regarded as a method for the management of medication risks. The process is initiated with the identification of a potential threat, after which evaluation and research are conducted, and actions are subsequently taken to reduce such risks. The final phase is considered to be the assessment of the efficacy of the process.

The implementation of PV is described as requiring the deployment of particular technologies through which communication between prescribers and end users is facilitated. Owing to possible new evidence or to insufficient measures having been applied, the overall risk management process is regarded as iterative. A drug safety concern is infrequently considered resolved, and the safety investigation is continued until the entire life cycle of the drug has been completed [90].

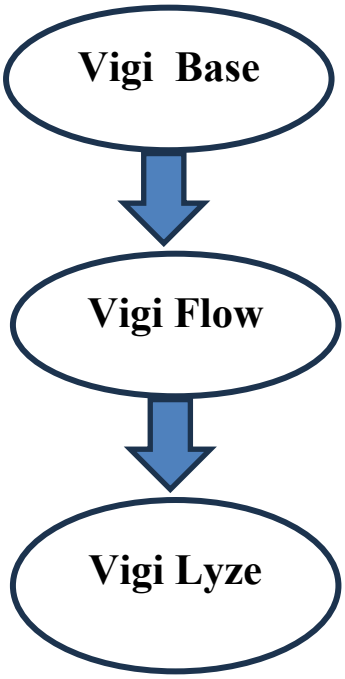

Figure.1: Pharmacovigilance tools to asses and detect the signals related to ADR

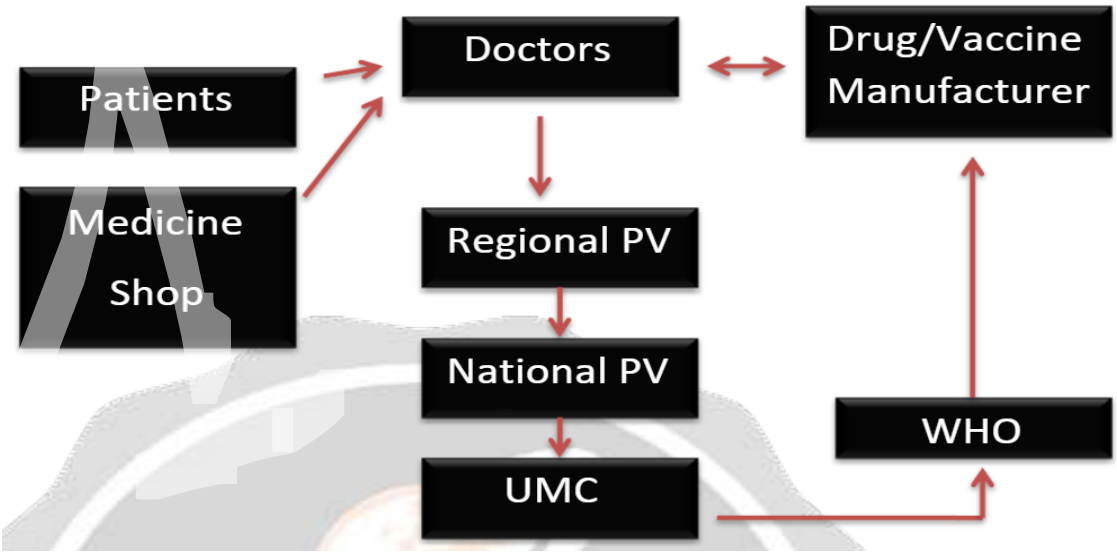

Figure 2: Flow of information among PV centre and global monitoring organisations by using Pharmacovigilance analytical tools [91].

Pharmacoepidemiology Study

The scientific study of the impact of the use of prescribed (and non-prescribed, such as over-the-counter) pharmaceuticals within a certain community is referred to as pharmacoepidemiology. Any consequences that may be observed, whether beneficial or harmful for the patient's health, are analyzed. The manner in which medications are actually utilized by patients is examined, including the way prescriptions are given by doctors and the way medications are taken daily by patients.

Instead of being based on statistical studies of small groups of individuals, reliance is placed on statistical analyses of large populations to draw relevant conclusions. This implies that trends are examined in larger groups of people who may or may not share certain traits, rather than the clinical history of a single patient. Epidemiology and pharmacoepidemiology are applied to the safety information obtained in order for its relevance to patients' actual use of medications to be better appreciated, even though such application is not the primary focus of standard pharmacovigilance services.

Each Safety Specification for a new medicine, which is included as a component of the Risk Management Plan and which summarizes what is known, what is unclear, and what information is lacking regarding the medicine's safety profile, is required to include epidemiological data. The creation of the Risk Management Plan itself is considered a component of pharmacovigilance service. Within the Risk Management Plan, a Pharmacovigilance Plan is contained, through which the

gaps in safety knowledge left by clinical trials are intended to be filled, and greater understanding of the known risks associated with a pharmaceutical is provided.

Pharmacoepidemiology studies are conducted to monitor patients over time and to determine their outcomes. These studies are typically carried out through registries in large groups of patients receiving the medication after marketing. To investigate additional safety signals that may emerge following the release of a drug, other types of pharmacoepidemiology studies may also be performed [92].

PHARMACOVIGILANCE IN DRUG REGULATION

Pharmacovigilance programs made strong by links with regulators. Regulators understand that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products.

Clinical trial regulation: In recent years there has been a substantial increase in the number of clinical trials in developed and developing countries. In their approval of clinical trials, regulatory bodies look at safety and efficacy of new products under investigation. Safety monitoring of medicines in common use should be an integral part of clinical practice. Education and training of health professionals in medicine safety, exchange of information between national pharmacovigilance centers, the coordination of such exchange, and the linking of clinical experience of medicine safety with research and health policy, all serve to enhance effective patient care. A regular flow and exchange of information in this way means that national pharmacovigilance programmes are ideally placed to identify gaps in our understanding of medicine-induced diseases [1].

Post marketing safety drug monitoring*:* These includes detection of drug interactions, measuring the environmental burden of medicines used in large populations, assessing the contribution of 'inactive' ingredients to the safety profile, systems for comparing safety profiles of similar medicines, surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones. The Council for International Organizations of Medical Sciences (CIOMS) report on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines.[16]

Pharmacovigilance in national drug Policy: The provision of good quality, safe and effective medicines and their appropriate use is the responsibility of national governments. Multidisciplinary collaboration is of great importance in particular, links need to be forged between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities, nongovernmental organizations (NGOs) and those professional associations having responsibility for education on rational use of medicines and pharmacotherapy monitoring.

Pharmacovigilance in Disease Control Public Health Programmes: The monitoring of medicine safety in countries where there is no regulatory or safety monitoring system in place, or in remote areas with little or no health care surveillance or infrastructure, has been identified as a matter for concern. The problems are especially apparent in situations that involve the use of medicines in specific communities, for example, for the treatment of tropical diseases such as malaria, leishmaniasis and schistosomiasis, and for the treatment of HIV/AIDS and tuberculosis. Pharmacovigilance should be a priority for every country with a public health disease control programs. [1]

Pharmacovigilance In Emergency Healthcare:

The lack of COVID-19 vaccines and medications during the early stages of the pandemic prompted a rush to repurpose medications that had already received approval for use in other situations. As a result, many medications (such as hydroxychloroquine, ivermectin, and azithromycin) have been used off-label to treat COVID-19 patients despite the fact that the supporting scientific evidence for their effectiveness was of low quality and was primarily derived from *in vitro* research, pharmacovigilance monitoring was considered essential in this context for the recognition of hazards associated with pharmaceuticals used off-label. The principle of "do not hurt first" was thereby emphasized, especially when little or no proof of benefits was available [93].

Azithromycin, a commonly prescribed macrolide antibiotic, was employed in this instance for the treatment of COVID-19 patients. Because of its known proarrhythmogenic activity, which was shown to be increased when it was combined with other medications recommended for COVID-19 treatment (such as hydroxychloroquine), warnings against its use—unless a risk of bacterial superinfection was present—were issued by regulatory bodies [94].

To combat the COVID-19 pandemic, expedited approval of medicines and vaccines was granted. The requirement for rapid collection of safety studies in post-marketing settings was thereby highlighted, so that major concerns could be identified and mitigated, ultimately ensuring patient safety. The significance of drug- and vaccine-related crisis communication to healthcare practitioners and patients was also emphasized, in order that informed treatment choices could be made and optimal use of medications and vaccines could be facilitated. In contrast, lives, as well as the reputation and confidence of regulators and other stakeholders, were placed at risk when ineffective communication with the public and medical services occurred. [95]

One medication that was given extensive attention for COVID-19 treatment was hydroxychloroquine. Despite the fact that its effectiveness was never established, it was praised by several prominent figures, including former U.S. President Donald J. Trump. As a result of such endorsements, a marked increase in hydroxychloroquine and chloroquine purchases and internet searches was observed in several observational studies. [96] This demonstrated that inappropriate medication use and the risk of serious adverse reactions could be increased by false information, particularly when disseminated by people in positions of authority [97].

Artificial Intelligence in Pharmacovigilance

Owing to the aggressive marketing of digital solutions designed to gather patient-derived data, a significant increase in the availability of healthcare data has been observed over the past few years, and further growth is anticipated in the near future. The opportunity to employ artificial intelligence (AI) methods for the enhancement of drug safety evaluation has been provided by massive electronic datasets [98].

Clinical research is increasingly being supported by information extraction, whereby pertinent concepts are gathered from largely unstructured sources through the use of natural language processing (NLP) methods and text mining. In pharmacovigilance, the collection of data on ADRs and drug–drug interactions from diverse textual sources is being facilitated by text mining and NLP techniques, thereby assisting academics and medical professionals in monitoring medication safety. In fact, the autonomous processing of ADRs is being developed by both governmental and private organizations through AI technologies [99].

In pharmacovigilance, machine learning and artificial intelligence are considered to be useful for [100].

1. the automatic completion of case report entry and processing tasks,
2. the identification of clusters of adverse events that represent symptoms of syndromes,
3. the conduct of pharmacoepidemiologic studies,
4. the connection of data through probabilistic matching within datasets, and
5. the prediction and prevention of adverse event spread through specific interventions [98–100].

Eco pharmacovigilance

Eco pharmacovigilance is defined as "the science and activities concerning detection, evaluation, understanding, and prevention of adverse effects or other difficulties related to the presence of medications in the environment, which influence both humans and other animal species." It is regarded as a crucial component in the reduction of risks associated with pharmaceutical pollutants entering the environment [101].

Pharmaceuticals are recognized as common environmental contaminants, and their entry into the environment is facilitated through a variety of channels, including patient excretion into the sewage system as parent molecules or active metabolites, releases by manufacturers or hospitals into wastewaters, and terrestrial depositions. The effects of pharmaceutical contamination on numerous animal species, including fish and vultures, have been examined in numerous studies [102].

By the identification, evaluation, and prevention of unfavorable consequences associated with the presence of medicines in the environment, an increasingly significant role in the control and minimization of the causes of pharmaceutical pollution is played by ecopharmacovigilance. Although the levels of pharmaceuticals detected in the environment were typically modest (ranging from mg/L to g/L), some potential direct and indirect dangers to humans are still required to be closely monitored [103].

It is well recognized that bacterial resistance may be increased by antibiotic exposure, and that pharmacological effects may be exercised by sex hormones even at relatively low concentrations. Additionally, particular susceptibility to low amounts of medication may be shown by certain demographics, including expectant mothers, children, and elderly patients. Therefore, the addressing of concerns relating to pharmaceutical pollution is considered one of the primary current objectives of pharmacovigilance [104].

Future Aspects

In terms of regulation, advancements have been made recently. However, the effects of these adjustments have not yet materialised, hence it has not yet been if it can be demonstrated that these innovations have improved conduct in pharmacovigilance. To further bolster the case. As a science, pharmacovigilance requires that academics create novel techniques that can improve the current system. The definition of pharmacovigilance as people currently know it has been about identifying new ADRs and, if essential, implementing the regulatory actions required to safeguard the public's health, such as revising the product's summary of characteristics (SPCs) or removing it from sale. The creation of data that can help a healthcare provider or patient make a decision about whether or not to utilise a drug has not received much attention. Pharmacovigilance has as one of its main objectives the gathering and dissemination of this data. Active surveillance is necessary to receive information about the safety of a drug at an early stage. When developing new methods for active post-marketing surveillance, one has to bear in mind the importance of being able to gather information in a timely manner. Spontaneous reporting has indeed been shown to be a useful tool in generating signals, but the relatively low number of

reports received for a specific association makes it less useful in identifying patient characteristics and risk factors that will contribute to the occurrence of an ADR in a certain person. This information is essential when it comes to a healthcare provider recommending whether or not a particular patient should use the drug in question. Additionally, when dealing with an ADR, patients and the treating physician may have queries like: Will this ADR go away? How long will this ADR last? How long till it resolves; what kind of care is required? The patient's role is gradually evolving. The modern patient is well informed about his illness and want to take an active role in his care, as opposed to being a patient with little power and information. As was already indicated, certain nations have recognised the value of patients as a source for data about adverse drug reactions. Patients in these nations have the choice to use the spontaneous reporting method to report ADRs. In the future, pharmacovigilance must focus on this group as a source of information in addition to the more conventional groups, such the health professionals, and this patient empowerment will continue [105,106].

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