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Pharmacovigilance Basics Overview and Application of Artificial Intelligence in Pharmacovigilance

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ABSTRACT

Pharmacovigilance is a process and science that monitors the safety of drugs and implements measures to reduce the risks of drugs and increase the benefits of drugs. The main reasons for using artificial intelligence in pharmacovigilance systems were initially based on faster processing of cases, elimination of human errors and standardization of processes.

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INTRODUCTION

Pharmacovigilance is the "process and science of monitoring the safety of pharmaceuticals and taking appropriate action to minimize risks and maximize therapeutic benefits." The words "pharmacovigilance" and "vigilia" are derived from the Greek and Latin words pharmakon, which means "medicine," and vigilia, which means "to watch." It is a planned activity in the sphere of professional healthcare with significant social and economic ramifications that aims to evaluate drug risk/benefit ratios, enhance patient safety, and enhance quality of life. The first recorded instance of pharmacovigilance occurred 169 years ago, on January 29, 1848, when Hannah Greener, a little child from the north of England, passed away following the administration of a chloroform anaesthetic prior to the excision of an infected toenail. Chloroform was a potent and safe anaesthetic that Sir James Simpson had discovered and introduced into therapeutic use.[1]

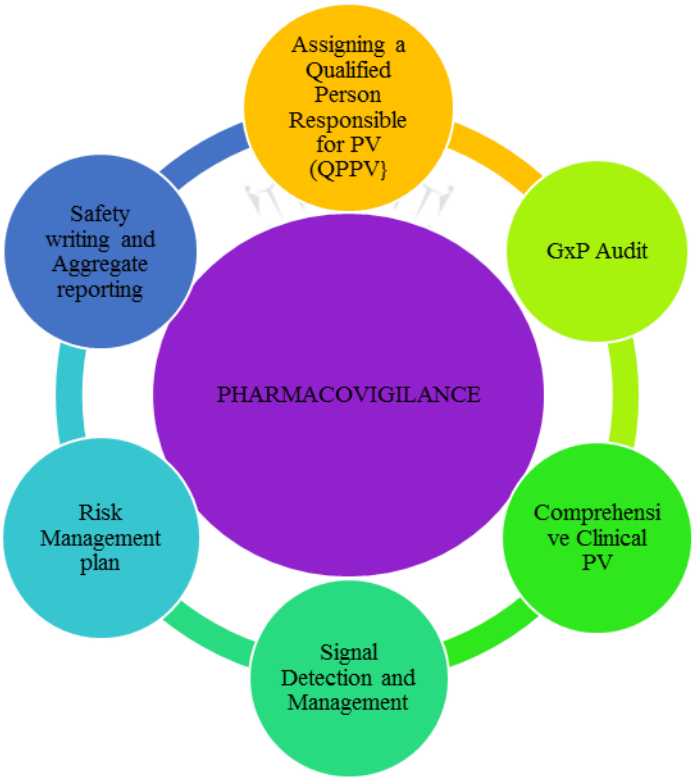

Figure No.1: Pharmacovigilance.

Purpose of Pharmacovigilance

Pharmacovigilance refers to research and practice related to identifying, evaluating, understanding, and mitigating adverse effects of drugs or other drug-related issues. Its concerns have recently been expanded to cover vaccines, blood products, biologicals,

traditional and complementary treatments, and herbals. There are other additional concerns that are relevant to science, medication errors, reports of lack of effectiveness, sub-standard quality, drug addiction and misuse, Case reports of acute and chronic poisoning, estimation of drug-related mortality, and adverse interactions of medications with substances, medications, and food are some of the issues that are covered by this study. The main responsibilities of NCC are to collect, analyse, and analyse data on adverse drug reactions (ADRs) and to recommend regulatory interventions to Central Drugs Standard Control Organisation (CDSCO).[2]

Scope of Pharmacovigilance

Since the WHO technical report from 1972, PV has grown significantly and is still a vibrant clinical and scientific field. Meeting the challenges posed by the increasing variety and potency of pharmaceutical and biological therapies, including vaccinations, which contain an inevitable and occasionally unanticipated potential for harm, has been crucial. However, there is a lower chance of danger when drugs are used by healthcare professionals who are knowledgeable and by people who are aware of and accountable for their medications. It is crucial to examine and effectively communicate side effects and toxicity to an audience with the ability to understand the facts when they do occur, especially when they were previously unknown in connection with the medication. This is a task of pharmacovigilance, for which much has already been achieved. But more is needed to integrate the discipline into clinical practice and public policy. To fulfil the PV obligations for its marketed products as per regulations, a pharmaceutical company in India has to essentially carry out activities such as collection, and expedited reporting of serious unexpected ADRs.[3]

WHO Collaborating Centre for International Drug Monitoring (WHO-UMC)

To supervise the specialized and scientific angles of the agenda, the WHO uniting Centre for International Drug Monitoring Uppsala Monitoring Centre (UMC) was substantiated in 1978. With the help of VigiBaseTM, the WHO Program for International Drug Monitoring (WHO PIDM), an international partnership, aims to enable prompt detection of medication-related safety issues. In 2022, the programme will have more than 170 full members and associate members, which will cover 99% of the global population.[4]

WHO-Uppsala Monitoring Centre (UMC) Causality Assessment Criteria

The following factors are part of the WHO-UMC method for assessing causality: undesirable event that can be predicted and the timing of it, Probable/likely-unlikely to be caused by other medications or illnesses, this could also be explained by drug use or another illness, The timing of an unlikely-unfavourable event can be used to explain it, but it's not impossible. more unclassified or conditional data is required to make an accurate assessment, Unclassifiable—An undesirable event is implied, but more information is required before a classification can be made.[5]

Terminologies

Pharmacovigilance has its own unique language that's important to understand. Utmost of the following terms are used within this composition and are peculiar to medicine safety, although some are used by other disciplines within the pharmaceutical ores as well.
• Adverse medicine response is goods arising when medicine given indeed in remedial cure either immunologically intermediated response or pharmacologically intermediated adverse response or idiosyncratic response due to the tricks of existence.
• Adverse event (AE) is a side effect with a medicine. By description, the unproductive relationship between the AE and the medicine is unknown.
• Benefits are generally expressed as the proven remedial good of a product but should also include the case's private assessment of its goods.

• Unproductive relationship is said to live when a medicine is allowed to have caused or contributed to the circumstance of an adverse medicine response.
• Clinical trial (or study) refers to a systematized program to determine the safety and/ or efficacity of a medicine (or medicines) in cases. The design of a clinical trial will depend on the medicine and the phase of its development.
• Control group is a group (or cohort) of individual cases that's used as a standard of comparison within a clinical trial. The control group may be taking a placebo (where no active medicine is given) or where a different active medicine is given as a comparator.
• Dechallenge and rechallenge relate to a medicine being stopped and renewed in a case, independently. A positive dechallenge has passed, for illustration, when an adverse event abates or resolves fully following the medicine's discontinuation. A positive rechallenge has passed when the adverse eventre-occurs after the medicine is renewed. Dechallenge and

rechallenge play an important part in determining whether an unproductive relationship between an event and a medicine exists.

• Effectiveness is the extent to which a medicine works under real world circumstances, i.e., clinical practice. efficacity is the extent to which a medicine works under ideal circumstances, i.e., in clinical trials.

• Event refers to an adverse event.[6]

Pharmacovigilance Setup

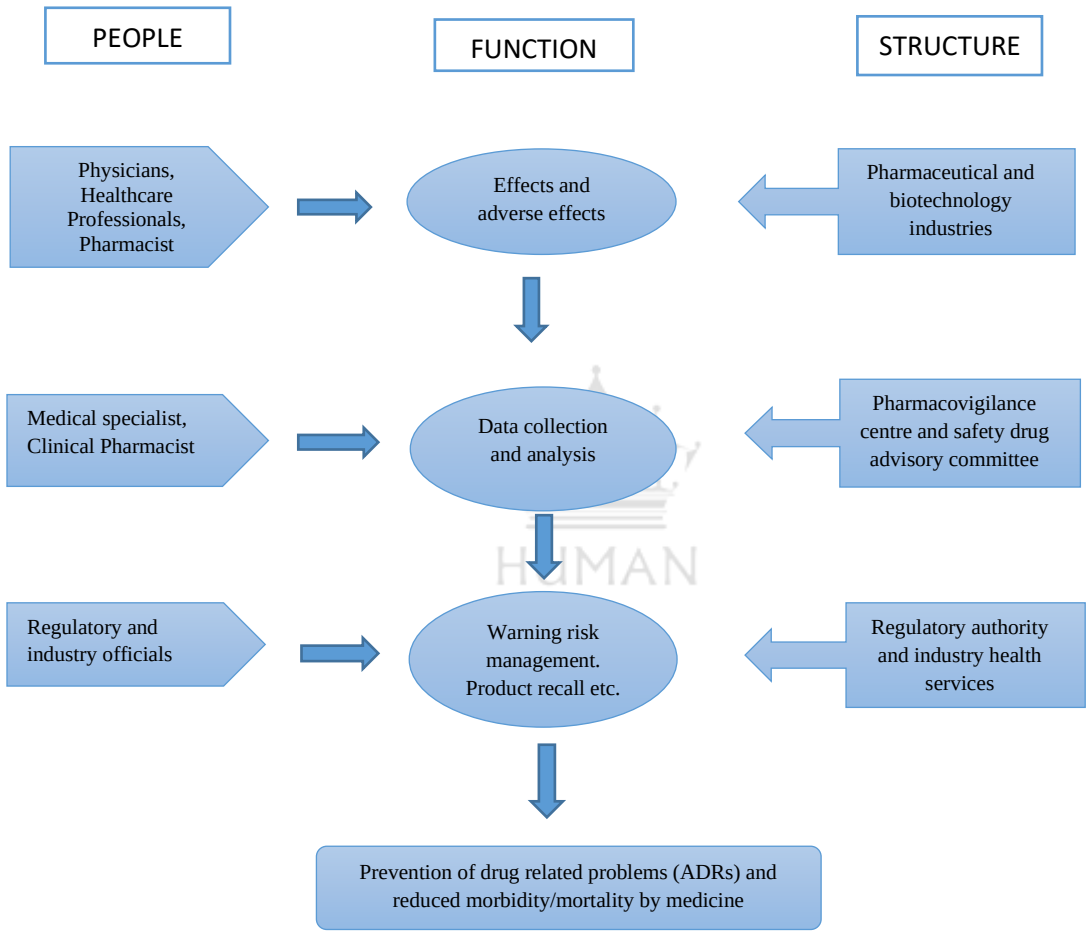

Figure No.2: A typical pharmacovigilance setup [7]

Role of Clinicians in Pharmacovigilance

By recognizing, managing, and reporting ADRs to the national pharmacovigilance centres, clinicians play a vital role in preventing ADRs (NPCs). Therapeutic judgement and the right drug selection for each patient are necessary for safe and sane drug prescription. Age,

medication error, polypharmacy, and patient-specific risk factors, such as comorbidities, are all variables that may raise the incidence of ADRs. Clinical pharmacologists must be familiar with the clinical pharmacological principles of ADRs, including their kinds, dose-relatedness, hypersensitivity reactions, time correlations, and risk factors, in order to recognise ADRs and distinguish them from other diseases or comorbidities. Long-term problems, such as atypical femoral fractures brought on by bisphosphonates, may, for instance, only manifest themselves after repeated exposure. Resuming drugs after stopping them can also make medical conditions worsen.[8]

Role of Pharmacist in Pharmacovigilance

In terms of their professional activity, pharmacists now focus more on the needs of their patients rather than just preparing or dispensing medications for the community. By preventing, identifying, documenting, and reporting ADRs, pharmacists help to ensure the safety of drugs. Despite the fact that a pharmacist's job in the pharmacovigilance department differs depending on the country, their professional obligations are the same everywhere. Although his or her clinical expertise may differ from that of a physician, a pharmacist has the potential to report ADRs on their own. One important step in advancing the avoidance of ADRs is to familiarise all clinical practitioners with the risk-benefit profile of medications. In the monitoring of pharmaceutical safety, pharmacists are essential. Pharmacists can be used to help monitor the safe and effective use of medicines that are now accessible, which undoubtedly includes the management of ADRs. It is important to value the valuable data the pharmacist gathers for pharmacovigilance. Pharmacists share resources, including databases, with clinical expertise as an open-arm. The development of newsletters and other publications by drug information and poison control centres, which are used by a variety of professions and professionals to disseminate drug alerts and other drug safety information, is a crucial task for pharmacists. Additionally, pharmacists need to be involved in gathering information that could be used to spur the start of long-term Pharmaco-epidemiological investigations. During the counselling session, pharmacists may ensure that the patients are in a supportive environment that helps to reduce medication errors, increase patient safety, and enhance quality of life. In research by Mohmoud *et al.*, just 23% of the participating pharmacists had experience with the ADR reporting process, while 77% had never done so. Lack of knowledge of the reporting process is a major factor in ADRs not being reported. In addition to reporting ADRs, pharmacists can also keep track of crucial patient safety files and records to maximise the benefits and minimise the risks of prescription use, as well as to stay

current on newer drug discoveries, regimens, and surgical techniques. A strong understanding of monitoring and counselling on the use of over-the-counter drugs should be possessed by pharmacists. [9]

Artificial Intelligence in Pharmacovigilance

Need of Artificial Intelligence in Pharmacovigilance

License holders must gather ADR data from pharmaceutical companies and provide it to the regional drug regulatory body. The detection and reporting of ADRs, the technical coding of AE, the preparation of safety individual reports, the assessment of seriousness, and the association with suspected drugs are the most crucial operations in the PV industry. The identification of ADRs necessitates new technologies because all of these rely on human interference, which takes time. An AI and ML (machine learning) system has been created by a multinational pharmaceutical corporation in partnership with a professional services firm to simplify the processing and upkeep of quality and compliance requirements. The amount of publicly accessible data is so large that it cannot be manually evaluated, which is where AI can be used to keep track of them.[10]

Different Definitions of "Ai" and Areas of Pharmacovigilance

The delineations and groups of AIS vary. The term" AI" might signify different effects to different people because it encompasses numerous distinct technologies and ways. For case, statistical models, a variety of algorithms, and tone- modifying systems are all exemplifications of artificial intelligence. While some would easily distinguish between AI and" robotization," others would see AI as an element of intelligent robotization and hyperactive robotization. For the time being, the most important thing to comprehend is that multitudinous approaches can be used to make AI in colorful ways. The crucial apologies for utilising AI within pharmacovigilance systems were originally grounded on faster processing of cases, elimination of mortal error, and standardization of processes. Another egregious provocations adding the cost effectiveness and gaining marketable edge compared to companies that calculate on old- fashioned processes dependent on offshoring mortal labour; interestingly enough, old-academy CROs and PV providers have little incitement to introduce as that would basically strike their entire business model, rendering them obsolete (this will be).

Average targets for AI in PV are the following:

• ICSR processing

• Aggregate reports

• Risk management

• Signal management

• Quality Management System (QMS)[11]

Artificial Intelligence in Pharmacovigilance

Categories

The Individual Case Safety Report (ICSR) is a document that follows a certain format and is used to record information in agreement with FDA conditions on adverse events (AEs), product- related problems, and client complaints. The National Coordination Centre for Pharmacovigilance Programme of India (NCC- PvPI) and the Central medicines norms Control Organization (CDSCO) both bear MAHs to expose ICSR of the drug that has been retailed in India. presently, NCC- PvPI, Ghaziabad has entered,441 ICSR that have been gathered and submitted. Eventually, these reports will be transmitted using VigiFlow software to WHO- UMC, Sweden. The running and processing of these reports is evolving into a tedious, time- consuming, and precious task due to the rise in ICSR reporting. As a result, PvPI may borrow the Machine Intelligence ways similar as AI for reducing pool, cost, and time for ICSR case processing.

There are two orders in AI in ICSR processing:

1. Insertion of structured and unshaped content insert information through XML, DOCX, Image, and PDF for reading the case. NLP and ML are used to prize ICSR information in a nonsupervisory biddable manner.

2. AI for decision- making the quality of ICSR is generally poor. thus, AI may play an important part in making the unrecorded or individual arbitrary AEs, medicine classifiers, correlation, etc.

PV's use of AI technologies makes it easier to extract correct data. Nearly every part of PV can be automated or facilitated by AI tools, including case processing and risk tracking,

which shortens the overall processing time. The following tools are some that are helpful in PV activities:

VigiBase

A PV database that stores the data in a structured, orderly fashion to make it simple to analyse recorded data The WHO-Adverse Reaction Terminology/Medical Dictionary for Regulatory Activities (MedDRA), WHO International Classification of Disease, and WHODrug are some of the medical and drug classifications that are connected to this system. VigiBase collected almost 20 million reports of negative medication effects (as of May 2019).

VigiAccess

It is a freely available web application that allows users to browse and quickly obtain data on adverse medication effects stored in VigiBase.

VigiLyze

It is a tool that can be used online to quickly and clearly review VigiBase and be further explored.

VigiFlow

It is a web-based ICSR management system for global drug surveillance that facilitates efficient data analysis through data collection, processing, and sharing. It is supported by WHO Drug and MedDRA.

VigiGrade

To assess the degree to which each case report's ordered, clinically important information is complete. This is mostly used to communicate with nations on the quality of their data.

VigiMatch

It is an algorithm that uses probabilistic pattern matching to find related individual case reports.

VigiRank

It is a novel technique for identifying statistical signals that take into account not only disproportionate reporting patterns but also the geographic distribution, completeness, and recentness of individual case reporting.

Electronically saved patient data makes it simple to identify AE and also includes details about the disease's phase, severity, and contributing variables. These data serve as an electronic health record and are a representation of the additional information that has been acquired and kept, which makes AI valuable.

Signal detection and its clinical evaluation are significant areas of PV. The Bayesian Confidence Propagation Neural Network is used by the WHO-UMC to find signals in the ICSR database. Depending on the accuracy of the data and the gravity of the events, more than one report may be necessary to identify the signal. Software for data mining, such as Empirica Signal and PV-analyzer, can also spot problems with drug safety. This signal production was controlled in India by CDSCO and NCC-PvPI utilising the database such as VigiBase. The signals are used by PvPI to review, identify, decide, and conclude the collected data from various national databases.

Benefits of Artificial Intelligence in Pharmacovigilance

The most important benefits of AI are reduced cycle times. Due to this method, the processing is spontaneous.

Improve the quality and accuracy of the information.

AI can handle or manage diverse types of incoming data formats.

It can be used for the identification of ADRs.

AI is useful to reduce the burden and time of case processing.

AI tools extract the information from the adverse drug event form and evaluate the case validity without the workforce.[12]

Specific Applications of AI in PV

Regulatory

Although AI has started to be used in many fields, it is still not developed enough to be widely used. With new drugs being rushed through the FDA's new regulatory channels, the COVID-19 pandemic illustrated the value of an agile, quick strategy.

The FDA published a five-year strategy to include AI into the pre-existing PV framework even before the epidemic. In order to increase the effectiveness and scientific value of the studies of ICSRs, the FDA is currently investigating ICSRs through their submission to FAERS. In addition to the few hundred thousand concerns from the general population, the FDA gets over 2 million reports from the industry each year.[13]

Clinical

A new drug must undergo 10–12 years of development before it can be sold, of which 5–7 years are required for the clinical trial stage. Patient recruiting and site selection are time-consuming tasks that, if not completed promptly, frequently result in clinical trial failure.

Pharmaceutical businesses are looking towards AI as a new strategy to not only cut expenses associated with research and development but also to avoid expensive mistakes.

Large amounts of data can be examined by AI using a data-driven methodology to pinpoint patient groupings who can profit from particular clinical research.

AI can assist in personalising data and ultimately have an impact on future research and development by optimising medical treatment through the use of mobile apps for assessments.[14]

Forms Of AI

Machine Learning

In machine learning, computers learn and modify themselves over time without being given explicit instructions. When new data becomes available, machine learning enables software to automatically learn from past data to improve behaviour and make new predictions.

This can be compared to how the brain is wired in humans based on particular experiences, which are then reviewed when a new experience is provided. Then, depending on all of their prior experiences, people make decisions on a daily basis in a subconscious manner.

In drug safety and PV, machine learning has many applications. Below are some examples:

Determining which patients will benefit more from a specific treatment.

Extracting notable data from ICSRs.

Predicting which patients are likely to fail at screening phases of a clinical trial.

Predicting which patients have a greater probability of discontinuing from a clinical trial.

Predicting which patients will experience an adverse event during a clinical trial.

Several machine learning models, including supervised learning, unsupervised learning, semi-supervised learning, reinforcement learning, natural language processing, and deep learning, can be used for PV analytics.[15]

Supervised Learning

Labels are used in the algorithm in supervised learning to correctly anticipate which label belongs to each individual component. In this type of AI, the system's input is labelled or tagged with the associated output tags. For instance, a set of factors is linked to patients who have suffered AEs and corresponding sets of variables are used for patients who do not experience an AE when forecasting which individuals would do so.

Unsupervised Learning

Unsupervised learning analyses unlabelled datasets using machine learning methods. Despite employing unlabelled data, the model searches for repeating patterns in the input data.

Labels are characterised as names for classifications or groups that we aim to anticipate. Labels can be "serious" or "nonserious," for instance, to indicate how serious an AE is. Here are several methods that can be applied:

Analysis of clusters. This particular data mining method groups unlabelled data based on how similar or dissimilar they are.

Detection of outliers. This particular data mining method looks for anomalies, occurrences, or observations that stand out considerably from the majority of the data.

Unsupervised and supervised learning are combined to create semi-supervised learning. Labelled data are pooled here. When there are incomplete data, predictive models can be developed with semi-supervised learning algorithms.[16]

Reinforcement Learning

When past experiences are drawn upon to make wise selections, this process is known as reinforcement learning. In the end, the algorithm is enhanced by past experiences with the aid of a continuous feedback loop. Because you are aiming toward focused treatments, focusing on particular patient characteristics and physical attributes might prevent AEs.

The policy, reward signal, value function, and environment model are the main components of this kind of learning system. It can be compared to a situation in a video game where a computer would try different solutions until it finds one that works.

The AI will either receive penalties or rewards for its activities, but the creator offers no tips or suggestions on how to win the game. As a result, the machine's inventiveness develops over time through several experiments. In the end, after numerous tries and errors AI will start from random trials to logical tactics and skills.[17]

Natural Language Processing (NLP)

Computers can now understand human language thanks to NLP. To build a programme that can analyse a lot of natural language data, the NLP technique uses computational linguistics.

This covers speech recognition, understanding, translation, interpretation, and language generation from sources including academic journals, medical records, and even social media. Although this idea has been around in the electronics sector since the 1960s, it has just recently been adopted by the PV sector in the last ten years.

Studying alleged ADRs that suggested sildenafil increased the likelihood of seizures through NLP has proven successful. Additionally, it has been applied to the development of predictive models for the identification of drug-induced repolarization problems, such as torsade de pointes and sudden cardiac death.[18]

Deep Learning

Deep learning is a sophisticated branch of machine learning that makes use of recurrent neural networks to simulate how the human brain processes information. In order to transmit information from one neuron to another, neural networks function similarly to how brain neurons do.

Deep learning comprises the sequential application of numerous machine learning layers, which calls for expert computational capacity.

Multiple data sets are processed simultaneously in deep learning. The outcome is then produced by revaluating and reprocessing these data sets several times.

The output of the previous layer serves as the foundation for each cycle of data assessment, which together produce the final desired output. Deep learning can be applied to drug discovery to anticipate structures that could have similar actions versus those that may not. In post market surveillance, deep learning can be used to perform comparative safety analyses and aid in clinical decision making.[19]

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