ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 08 | August - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

THE ROLE OF PHARMACOVIGILANCE IN REDUCING ADVERSE DRUG REACTIONS AND DRUG SAFETY IN ASSOCIATION WITH ARTIFICIAL INTELLEGENCE AND MACHINE LEARNING

Pharmaceutical Science

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ABSTRACT

Pharmacovigilance (PV), also known as drug safety, is the pharmaceutical science relating to the "collection, detection, assessment, monitoring, and prevention" of adverse effects with pharmaceutical products.Pharmacovigilance heavily focuses on adverse drug reactions (ADR), which are defined as any response to a drug which is noxious and unintended. In 2010, the European Union expanded PV to includemedication errors such as overdose, misuse, and abuse of a drug as well as drug exposure during pregnancy and breastfeeding. These are monitored even in the absence of an adverse event; because they may result in an adverse drug reaction.Patient and healthcare provider reports as well as other sources such as cases reported in medical literature, play a critical role in providing the data necessary for pharmacovigilance to take place. In order to market or to test a pharmaceutical product in most countries, adverse event data received by a pharmaceutical company must be submitted to the national drug regulatory authority. Artificial intelligence allows for the processing and analysis of large amounts of data and can be applied to various disease states. The artificial intelligence and machine learning models can optimize pharmacovigilance processes and provide a more efficient way to analyze information relevant to safety, even though more research is needed to identify if this optimization has an impact on the quality of safety analyses. It is expected that its use will increase in the near future, particularly with its role in the prediction of side effects and ADRs.

KEYWORDS

Pharmacovigilance, ADR, Drug safety, Artificial intelligence, Machine learning

INTRODUCTION

Pharmacovigilance also known as drug safety, is the pharmaceutical science relating to the "collection, detection, assessment, monitoring, and prevention" of adverse effects with pharmaceutical products.

The etymological roots for the word "pharmacovigilance" are: *pharmakon* (Greek for drug) and *vigilare* (Latin for to keep watch). As such, pharmacovigilance heavily focuses on adverse drug reactions (ADR), which are defined as any response to a drug which is noxious and unintended. That definition includes lack of efficacy: that means that the doses normally used for prevention, diagnosis, or treatment of a disease—or, especially in the case of device, for the modification of physiological disorder function. In 2010, the European Union expanded PV to includemedication errors such as overdose, misuse, and abuse of a drug as well as drug exposure during pregnancy and breastfeeding. These are monitored even in the absence of an adverse event, because they may result in an adverse drug reaction.The US FDA has long considered such criteria to conform to reportable and collectible PV standards[1].

Patient and healthcare provider reports (via pharmacovigilance agreements or national mandated reporting laws), as well as other sources such as cases reported in medical literature, play a critical role in providing the data necessary for pharmacovigilance to take place. In order to market or to test a pharmaceutical product in most countries, adverse event data received by the license holder (usually a pharmaceutical company) must be submitted to the national drug regulatory authority.

Ultimately, pharmacovigilance is concerned with identifying the hazards associated with pharmaceutical products and with minimizing the risk of any harm that may come to patients. Companies must conduct a comprehensive drug safety and pharmacovigilance audit to assess their compliance with local, regional, national, or international laws and regulations. This includes ongoing collection of safety data after a product is approved for marketing.

ADVERSE EVENT REPORTIN

The activity that is most commonly associated with pharmacovigilance (PV), and which consumes a significant number of resources for drug regulatory authorities (or similar government agencies) and drug safety departments in pharmaceutical companies, is that of adverse event reporting. Adverse event (AE) reporting involves the receipt, triage, data entry, assessment, distribution, reporting (if appropriate), and archiving of AE data and documentation. The source of AE reports may include: spontaneous reports from healthcare professionals or patients (or other intermediaries); solicited reports from patient support programs; reports from clinical or post-marketing studies; reports from literature sources; reports from the media (including social media and websites); and reports reported to drug regulatory authorities themselves. For pharmaceutical companies, AE reporting is a regulatory requirement in most countries. AE reporting also provides data to these companies and drug regulatory authorities that play a key role in assessing the risk-benefit profile of a given drug[2-3].

The following are several facets of AE reporting:

Individual case safety report

One of the fundamental principles of adverse event reporting is the determination of what constitutes an individual case safety report. During the triage phase of a potential adverse event report, it is important to determine if the "four elements" of a valid individual case safety report are present: (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect drug, and (4) an adverse event.

If one or more of these four elements is missing, the case is not a valid individual case safety report. Although there are no exceptions to this rule there may be circumstances that may require a judgment call. For example, the term "identifiable" may not always be clear-cut. If a physician reports that he/she has a patient X taking drug Y who experienced Z (an AE), but refuses to provide any specifics about patient X, the report is still a valid case even though the patient is not specifically identified. This is because the reporter has first-hand information about the patient and is *identifiable* (i.e. a real person) to the physician. Identifiability is important so as not only to prevent duplicate reporting of the same case, but also to permit follow-up for additional information.

The concept of identifiability also applies to the other three elements. Although uncommon, it is not unheard of for fictitious adverse event "cases" to be reported to a company by an anonymous individual (or on behalf of an anonymous patient, disgruntled employee, or former employee) trying to damage the company's reputation or a company's product. In these and all other situations, the source of the report should be ascertained (if possible). But anonymous reporting is also important, as whistle blower protection is not granted in all countries. In general, the drug must also be specifically named. Note that in

different countries and regions of the world, drugs are sold under various trade names. In addition, there are a large number of generics which may be mistaken for the trade product. Finally, there is the problem of counterfeit drugs producing adverse events. If at all possible, it is best to try to obtain the sample which induced the adverse event, and send it to the European Medicines Agency, FDA or other government agency responsible for investigating AE reports[4].

If a reporter can't recall the name of the drug they were taking when they experienced an adverse event, this would not be a valid case. This concept also applies to adverse events. If a patient states that they experienced "symptoms", but cannot be more specific, such a report might technically be considered valid, but will be of very limited value to the pharmacovigilance department of the company or to drug regulatory authorities.

ACTIVITIES INVOLVED IN PHARMACOVIGILANCE

1. Case-control study (*Retrospective study*)
2. Prospective study (*Cohort study*).
3. Population statistics. And
4. Intensive event report.
5. The spontaneous report in the case is the population of the single case report.

CODING OF ADVERSE EVENT

Adverse event coding is the process by which information from an AE reporter, called the "verbatim", is coded using standardized terminology from a medical coding dictionary, such as MedDRA (the most commonly used medical coding dictionary). The purpose of medical coding is to convert adverse event information into terminology that can be readily identified and analyzed. For instance, Patient 1 may report that they had experienced "a very bad headache that felt like their head was being hit by a hammer" [Verbatim 1] when taking Drug X. Or, Patient 2 may report that they had experienced a "slight, throbbing headache that occurred daily at about two in the afternoon" [Verbatim 2] while taking Drug Y. Neither Verbatim 1 nor Verbatim 2 will exactly match a code in the MedDRA coding dictionary. However, both quotes describe different manifestations of a headache. As a result, in this example both quotes would be coded as PT Headache (PT = Preferred Term in MedDRA)[5].

Seriousness determination

Although somewhat intuitive, there are a set of criteria within pharmacovigilance that are used to distinguish a serious adverse event from a non-serious one. An adverse event is considered serious if it meets one or more of the following criteria:

1. results in death, or is life-threatening;
2. requires inpatient hospitalization or prolongation of existing hospitalization;
3. results in persistent or significant disability or incapacity;
4. results in a congenital anomaly (birth defect); or
5. Is otherwise "medically significant" (i.e., that it does not meet preceding criteria, but is considered serious because treatment/intervention would be required to prevent one of the preceding criteria.).

A side from death, each of these categories is subject to some interpretation. Life-threatening, as it used in the drug safety world, specifically refers to an adverse event that places the patient at an *immediate risk of death*, such as cardiac or respiratory arrest. By this definition, events such as myocardial infarction, which would be hypothetically life-threatening, would not be considered life-threatening unless the patient went into cardiac arrest following the MI. Defining what constitutes hospitalization can be problematic as well. Although typically straightforward, it's possible for a hospitalization to occur even if the events being treated are not serious. By the same token, serious events may be treated without hospitalization, such as the treatment of anaphylaxis may be successfully performed with epinephrine. Significant disability and incapacity, as a concept, is also subject to debate. While permanent disability following a stroke would no doubt be serious, would "complete blindness for 30 seconds" be considered "significant disability"? For birth defects, the seriousness of the event is usually not in dispute so much as the attribution of the event to the drug. Finally, "medically significant events" is a category that includes events that may be always serious, or sometimes serious, but will not fulfill any of the other criteria. Events such as cancer might always be considered serious, whereas liver disease, depending on its Common Terminology Criteria for Adverse Events (CTCAE) grade—Grades 1 or 2 are generally considered non-serious and Grades 3-5 may be considered serious[6-7].

Expedited reporting

This refers to individual case safety reports that involve a serious and unlisted event (an event not described in the drug's labeling) that is considered related to the use of the drug (US FDA). (Spontaneous reports are typically considered to have a positive causality, whereas a clinical trial case will typically be assessed for causality by the clinical trial investigator and/or the license holder.) In most countries, the time frame for reporting expedited cases is 7/15 calendar days from the time a drug company receives notification (referred to as "Day 0") of such a case. Within clinical trials such a case is referred to as a SUSAR (a Suspected Unexpected Serious Adverse Reaction). If the SUSAR involves an event that is life-threatening or fatal, it may be subject to a 7-day "clock". Cases that do not involve a serious, unlisted event may be subject to non-expedited or periodic reporting.

Clinical trial reporting

Also known as AE (adverse event) or SAE (serious AE) reporting from clinical trials, safety information from clinical studies is used to establish a drug's safety profile in humans and is a key component that drug regulatory authorities consider in the decision-making as to whether to grant or deny market authorization (market approval) for a drug. AE reporting occurs when study patients (subjects, participants) experience any kind of "untoward" event during the conducting of clinical trials. Non-serious adverse events are typically captured separately at a level lower than pharmacovigilance. AE and SAE information, which may also include relevant information from the patient's medical background, are reviewed and assessed for both causality and degree of seriousness by the study investigator. This information is forwarded to a sponsoring entity (typically a pharmaceutical company or academic medical center) that is responsible for the reporting of this information, as appropriate, to drug regulatory authorities[8].

Spontaneous reporting

Spontaneous reports are termed spontaneous as they take place during the clinician's normal diagnostic appraisal of a patient, when the clinician is drawing the conclusion that the drug may be implicated in the causality of the event.

Spontaneous reporting system (SRS) relies on vigilant physicians and other healthcare professionals who not only generate a suspicion of an adverse drug reaction, but also report it. It is an important source of regulatory actions such as taking a drug off the market or a label change due to safety problems. Spontaneous reporting is the core data-generating system of international pharmacovigilance, relying on healthcare professionals (and in some countries consumers) to identify and report any adverse events to their national pharmacovigilance center, health authority (such as the European Medicines Agency or FDA), or to the drug manufacturer itself.Spontaneous reports are, by definition, submitted voluntarily although under certain circumstances these reports may be encouraged, or "stimulated", by media reports or articles published in medical or scientific publications, or by product lawsuits. In many parts of the world adverse event reports are submitted electronically using a defined message standard.

One of the major weaknesses of spontaneous reporting is that of under-reporting, where, unlike in clinical trials, less than 100% of those adverse events occurring are reported. Further complicating the assessment of adverse events, AE reporting behavior varies greatly between countries and in relation to the seriousness of the events, but in general probably less than 10% (some studies suggest less than 5%) of all adverse events that occur are actually reported. The rule-of-thumb is that on a scale of 0 to 10, with 0 being least likely to be reported and 10 being the most likely to be reported, an uncomplicated non-serious event such as a mild headache will be closer to a "0" on this scale, whereas a life-threatening or fatal event will be closer to a "10" in terms of its likelihood of being reported. In view of this, medical personnel may not always see AE reporting as a priority, especially if the symptoms are not serious. And even if the symptoms are serious, the symptoms may not be recognized as a possible side effect of a particular drug or combination thereof. In addition, medical personnel may not feel compelled to report events that are viewed as expected. This is why reports from patients themselves are of high value. The

confirmation of these events by a healthcare professional is typically considered to increase the value of these reports. Hence it is important not only for the patient to report the AE to his health care provider (who may neglect to report the AE), but also report the AE to both the biopharmaceutical company and the FDA, European Medicines Agency.This is especially important when one has obtained one's pharmaceutical from a compounding pharmacy.

As such, spontaneous reports are a crucial element in the worldwide enterprise of pharmacovigilance and form the core of the World Health Organization Database, which includes around 4.6 million reports (January 2009),growing annually by about 250,000.

Aggregate reporting

Aggregate reporting, also known as periodic reporting, plays a key role in the safety assessment of drugs. Aggregate reporting involves the compilation of safety data for a drug over a prolonged period of time (months or years), as opposed to single-case reporting which, by definition, involves only individual AE reports. The advantage of aggregate reporting is that it provides a broader view of the safety profile of a drug. Worldwide, the most important aggregate report is the Periodic Safety Update Report (PSUR) and Development Safety Update Report (DSUR). This is a document that is submitted to drug regulatory agencies in Europe, the US and Japan (ICH countries), as well as other countries around the world. The PSUR was updated in 2012 and is now referred to in many countries as the Periodic Benefit Risk Evaluation report (PBRER). As the title suggests, the PBRER's focus is on the benefit-risk profile of the drug, which includes a review of relevant safety data compiled for a drug product since its development.

Causality assessment

One of the most important, and challenging, problems in pharmacovigilance is that of the determination of causality. Causality refers to the relationship of a given adverse event to a specific drug. Causality determination (or assessment) is often difficult because of the lack of clear-cut or reliable data. While one may assume that a positive temporal relationship might "prove" a positive causal relationship, this is not always the case. Indeed, a "bee sting" Adverse Event — where the AE can clearly be attributed to a specific cause — is by far the exception rather than the rule. This is due to the complexity of human physiology as well as that of disease and illnesses. By this reckoning, in order to determine causality between an adverse event and a drug, one must first exclude the possibility that there were other possible causes or contributing factors. If the patient is on a number of medications, it may be the combination of these drugs which causes the AE, and not any one individually. There have been a number of recent high-profile cases where the AE led to the death of an individual. The individuals were not overdosed with any one of the many medications they were taking, but the combination there appeared to cause the AE. Hence it is important to include in your/one's AE report, not only the drug being reported, but also all other drugs the patient was also taking.

For instance, if a patient were to start Drug X and then three days later were to develop an AE, one might be tempted to attribute blame Drug X. However, before that can be done, the patient's medical history would need to be reviewed to look for possible risk factors for the AE. In other words, did the AE occur with the drug or *because* of the drug? This is because a patient on any drug may develop or be diagnosed with a condition that could not have possibly been caused by the drug. This is especially true for diseases, such as cancer, which develop over an extended period of time, being diagnosed in a patient who has been taken a drug for a relatively short period of time. On the other hand, certain adverse events, such as blood clots (thrombosis), can occur with certain drugs with only short-term exposure. Nevertheless, the determination of risk factors is an important step of confirming or ruling-out a causal relationship between an event and a drug.

Often the only way to confirm the existence of a causal relationship of an event to a drug is to conduct an observational study where the incidence of the event in a patient population taking the drug is compared to a control group. This may be necessary to determine if the background incidence of an event is less than that found in a group taking a drug. If the incidence of an event is statistically significantly higher in the "active" group versus the placebo group (or other control group), it is possible that a causal relationship may exist to a drug, unless other confounding factors may exist[9].

Risk management plans

A risk management plan is a documented plan that describes the risks (adverse drug reactions and potential adverse reactions) associated with the use of a drug and how they are being handled (warning on drug label or on packet inserts of possible side effects which if observed should cause the patient to inform/see his physician and/or pharmacist and/or the manufacturer of the drug and/or the FDA, European Medicines Agency and Indian medical agency). The overall goal of a risk management plan is to assure a positive risk-benefit profile once the drug is (has been) marketed. The document is required to be submitted, in a specified format, with all new market authorization requests within the European Union (EU). Although not necessarily required, risk management plans may also be submitted in countries outside the EU.

Risk/benefit profile of drugs

Pharmaceutical companies are required by law in most countries to perform clinical trials, testing new drugs on people before they are made generally available. This occurs after a drug has been pre-screened for toxicity, sometimes using animals for testing. The manufacturers or their agents usually select a representative sample of patients for whom the drug is designed – at most a few thousand – along with a comparable control group. The control group may receive a placebo and/or another drug, often a so-called "gold standard" that is "best" drug marketed for the disease.

- The purpose of clinical trials is to determine
- if a drug works and how well it works
- if it has any harmful effects, and
- if it does more good than harm, and how much more? If it has a potential for harm, how probable and how serious is the harm?

IV. Need Of Artificial Intelligence In Pharmacovigilance

- Pharmacovigilance was designed mainly for patient safety whoever limited exposed to treatment drugs during clinical trials and research. This makes it possible to observe drug profiles for a prolonged period and use.

- It also includes certain groups such as geriatric population, racial groups, pediatric population and pregnant women, and also the incomplete data from long-term drug exposure makes it mandatory to perform PV studies.

- The approval of life saving drugs such as anticancer drugs, antitubercular, and antiretroviral drugs is based on fast track system so these drugs could be easily available for the patients and PV performs the assessment, communication of the risk, and effectiveness of these medications.

- In developing countries, PV is still a new concept with low preference. Worldwide the countries are raising the issues in concern for the need of systems to monitor the safety of drug postmarketing.

- Reporting of adverse drug reaction (ADR) is mainly done through spontaneous reporting or by pharmacoepidemiological methods that use systematic collection and analysis of adverse events (AE) associated with the use of drugs. It is also done by Adverse Drug Reaction Monitoring Centres and marketing authorization holder (MAH) industries to solve emerging problems, record signals, and communicate to minimize or prevent harm.

- Nowadays, drug safety is a major threat after launching the new drug to the market. During the clinical trial or after marketing, the major source of erosion is unpredictable toxicities that cause morbidity and mortality from normal dose of the drug. As per the record from 2008 to 2017, the Food and Drug Administration (FDA) approved 321 novel drugs. At the same time FDA, AE Reporting System has reported a total of >10 million AE reports in which 5.8 million were recorded as serious, and 1.1 million were death reports.

- ADR data need to be collected by license holder that should be from pharmaceutical company and submitted to the local drug regulatory authority. The most important operation in PV industry is detection and reporting of ADRs, coding of adverse events (AE) in technical terms, preparing safety individual reports, assessment of seriousness, and relationship with suspected drug. All of these depend on the human interference, which is time-consuming; and

hence, the detection of ADRs requires a new technology.

- A multinational pharmaceutical company in collaboration with a professional services company has developed an AI and Machine learning (ML) system to facilitate the processing and maintenance of quality and compliance standards. The globally available data are so vast that it cannot be analyzed manually where AI becomes useful to track them. AI techniques play a significant role in the area of drug design and identification of AEs of pharmaceutical products.

V. Artificial Intelligence In Pharmacovigilance

- Individual Case Safety Report (ICSR) is a document in a specific format for recording information with the use of FDA regulations to provide the information on AEs, product-related issues, and consumer reports.

- The Central Drugs Standards Control Organization (CDSCO) has made it mandatory for the marketing authorization holder (MAHs) to report ICSR of the marketed drug in India to National Coordination Center for PharmacovigilanceProgramme of India (NCC-PvPI) as well as to them. Currently, 64,441 ICSR has been collected and submitted to NCC-PvPI, Ghaziabad. Finally, these reports will be sent to WHO-UMC, Sweden, through VigiFlowsoftware.Because of increasing number of ICSR reporting, the handling and the processing of these reports is becoming tedious and time-consuming job including the high cost.

Therefore, PvPI may also adopting the Machine Intelligence techniques such as AI for reducing workforce, cost, and time for ICSR case processing.

There are two categories in AI in ICSR (Individual Case Safety Report) processing:

- **Insertion of structured and unstructured content:** Insert information through XML, DOCX, Image, and PDF for reading the case. NLP and ML are used to extract ICSR information in a regulatory compliant manner

- **AI for decision-making:** The quality of ICSR is usually poor. Therefore, AI may play an important role in making the unlisted or individual random AEs, drug classifiers, correlation, etc.

- AI technologies in PV are very helpful in the extraction of accurate information. AI tools can automate or facilitate almost every aspect of PV in case processing, risk tracking, which reduces the total processing time.These are some tools which are useful in PV activities:

VigiBase

- A PV database that records the information in a structured and ordered form to allow easy analysis of recorded data. This system is related to medical and drug classifications, including the WHO-Adverse Reaction Terminology/Medical Dictionary for Regulatory Activities (MedDRA), WHO International Classification of Disease, and WHODrug. Over 20 million reports of adverse drug effect were recorded by VigiBase (as of May 2019).

Vigi Access

- It is a publicly accessible web application to browse and access the data of adverse drug effects easily through VigiBase.

Vigi Lyze

- It is an online resource that provides a clear and quick review of VigiBase which can be explored online for further analysis.

Vigi Flow

It is a web-based ICSR management system for international drug monitoring by collection, processing, and sharing of data to facilitate effective data analysis, which is supported by WHO Drug and MedDRA.

Vigi Grade

- To measure the completeness score of clinically relevant information in ordered format on the individual case report. This is mainly used as a part of communication with countries on data quality.

Vigi Match

- It is an algorithm to detect the similar individual case report by the use of probabilistic pattern matching.

Vigi Rank

It is a novel method to detect the statistical signals which is not just for disproportionate reporting patterns but also for the completeness, recency, and geographic spread of individual case reporting. The patient data stored electronically is easy to diagnose AE, with additionally provided information as symptoms of disease, phase, and severity of the disease and contributing factors. These data act as electronic health record and it represents the stored and collected additional information that generates the usefulness of AI.

- An important domain of PV is signal detection and its clinical assessment. The WHO-UMC uses the Bayesian Confidence Propagation Neural Network to detect signal in ICSR database. More than a single report is required to detect the signal; it depends on the quality of the information and severity of the events.

- Data mining software (Empirica Signal, PV-analyzer) is also detect the drug safety issue. In India, CDSCO along with NCC-PvPI regulated this signal generation using 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(AI) 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.

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