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Review Article

A Review on Pharmacovigilance: Current Trends and Future Directions

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ABSTRACT

Pharmacovigilance plays a vital role in ensuring the safety and efficacy of medications. This review provides an overview of current trends and future directions in pharmacovigilance, highlighting advancements in signal detection, risk management, and minimization strategies. The article discusses the increasing importance of real-world evidence, artificial intelligence, and machine learning in pharmacovigilance. Regulatory updates, including the implementation of the European Medicines Agency's (EMA) Good Pharmacovigilance Practices and the US Food and Drug Administration's (FDA) Safety Information and Adverse Event Reporting regulations, are also examined. Furthermore, this review explores emerging challenges and opportunities in pharmacovigilance, such as:

- The growing need for personalized medicine safety monitoring
- The integration of pharmacogenomics and precision medicine
- The impact of social media and digital health technologies on adverse event reporting
- The evolving role of patients and healthcare professionals in pharmacovigilance.

INTRODUCTION

Monitoring the safety of medicines is an ongoing and dynamic process throughout the entire drug lifecycle. During drug development, safety is assessed in various stages. In preclinical studies, the main aim of safety evaluation is to identify a safe dose for humans and establish safety parameters for clinical monitoring. In the clinical phase, Phase I studies aim to determine the tolerability of the dose range expected for future studies involving healthy volunteers; Phase II studies focus on identifying appropriate drug doses for patients with specific diseases or conditions, while Phase III trials are crucial for refining the understanding of the drug's benefit-risk profile and identifying rarer adverse drug reactions. Despite the rigorous nature of drug safety evaluations, pre-marketing clinical trials have inherent limitations that prevent a comprehensive assessment of the drug's safety profile. These trials are conducted with a limited number of patients who are selected based on strict eligibility criteria, which do not

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fully reflect real-world populations, and have a limited duration, hindering the detection of rare and long-term adverse effects. Post-marketing assessment of medicines is crucial for accurately defining their safety profiles in real-world contexts and addressing the evidence gaps left by pre-marketing studies. In the realm of drug safety and regulation, several challenges will need to be addressed in the near future. Firstly, the COVID-19 pandemic has underscored the importance of pharmacovigilance and effective risk communication during public health emergencies. Secondly, advancements in methodologies, such as machine learning and the availability of extensive electronic healthcare data, present opportunities to enhance the evaluation of drug benefit-risk profiles in real-world settings. Additionally, the rise of innovative therapeutics, including advanced therapy medicinal products, digital therapeutics, and vaccines developed using cutting-edge technologies, has necessitated specialized pharmacovigilance monitoring. These products have increasingly entered the market, often through accelerated approval pathways. Below, some of the challenges and future opportunities in this area are briefly outlined.

Current Trends In Pharmacovigilance:

The rapid advancements in medical and pharmaceutical sciences have led to the development of modern medicines that effectively prevent, control, and manage various diseases. Despite their numerous benefits, adverse reactions to medications are common and are linked to many newly developed drugs. These adverse effects can range from mild side effects to severe hypersensitivities, often resulting in new illnesses, disabilities, or even death. Over the years, the prevalence of adverse drug reactions has increased, and in many countries, they are among the leading causes of mortality.

Therefore, it is essential to have a well-organized system for the continuous monitoring and assessment of medicine safety. Pharmacovigilance serves this purpose. While the concept of pharmacovigilance is not new, its origins date back over 50 years. The thalidomide tragedy of 1961 highlighted the critical need for assessing the adverse effects of drugs. Between 1965 and 1970, following several meetings and resolutions, the International Drug Monitoring Program was established by the World Health Assembly. The World Health Organization (WHO) defines pharmacovigilance as "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems."

Pharmacovigilance plays a vital role in promoting and enhancing public health. Its key objectives include:

- Identifying risks associated with medication use among patients.
- Participating in the comparative assessment of potential benefits and adverse effects of drugs to optimize their use.
- Promoting the safe, effective, and rational use of medicines.
- Raising awareness among patients and the general public about safe medication practices through effective communication.

Achieving these goals requires collaborative efforts and contributions from various stakeholders in pharmacovigilance. Input from government bodies, academia, pharmaceutical and medical associations, healthcare professionals, and the media is essential for improving the management of risks related to medication use.

Pharmacovigilance is integral to several aspects of healthcare management for the general population. Key areas of incorporation include:

National Drug Policy: For many countries, establishing drug regulatory bodies with dedicated pharmacovigilance programs is the first step in ensuring the safe and rational use of medicines. These programs monitor and assess adverse drug

reactions, communicating findings to relevant stakeholders.

Drug Regulation: Drug regulatory authorities go beyond merely approving the manufacture and marketing of new medicines. In collaboration with pharmacovigilance programs, they ensure ongoing safety by conducting post-marketing surveillance and analyzing the benefits and harms of drugs in broader populations.

Clinical Practice: Efficient information exchange between pharmacovigilance centers and clinical practitioners is crucial for maintaining high-quality healthcare. Pharmacovigilance programs support healthcare professionals by keeping them updated on the adverse outcomes associated with medications.

Public Health Programs: Many underdeveloped countries struggle with inadequate healthcare infrastructure and face high prevalence rates of tropical infectious diseases. In these settings, multiple medications may be administered simultaneously without sufficient awareness of potential adverse drug reactions or interactions. Pharmacovigilance programs provide training for healthcare providers and enhance awareness of safe medication use.

Several national and international organizations offer guidelines for effective pharmacovigilance program implementation. These agencies serve as valuable resources for managing the risks associated with medication use. The World Health Organization (WHO) maintains a comprehensive database on pharmacovigilance implementation, emphasizing its role in ensuring medication safety in public health. Additionally, the United States Food and Drug Administration (USFDA) published guidelines in 2005 on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment for marketed drugs. Despite their usefulness, access to information from these sources is often limited to a small segment of society, highlighting the need for a platform that provides the latest scientific findings, regulations, reviews, and guidelines on safe medication use to the broader public.

The Journal of Pharmacovigilance is a significant step in this direction. This publication aims to gather and disseminate scientific information on a wide range of unintended drug effects, including side effects, adverse drug reactions, drug interactions, and both short- and long-term toxicities. As an open-access, peer-reviewed journal, it ensures that all published information is immediately and freely accessible to the public.

As we embark on this journey, I invite members of academia, industry, government, and the healthcare community to actively contribute their opinions, scientific findings, and expert reviews to The Journal of Pharmacovigilance. I firmly believe that this journal will significantly enhance public awareness regarding the detection, assessment, understanding, and prevention of adverse effects associated with medicines.

Origin Of Pharmacovigilance:

A significant breakthrough in pharmacovigilance emerged following a tragic incident in 1937, when approximately 105 children and 71 adults died after consuming a syrup containing sulphonamide and diethylene glycol, the latter being identified as the culprit. Sulphonamide had been used since 1932 for treating streptococcal infections and was reformulated as a syrup with diethylene glycol as the solvent. Although sulfanilamide (Prontosil) had been safely used since 1932, the syrup's safety was not assessed prior to its release. This tragedy prompted the U.S. Congress to enact the Food, Drug, and Cosmetic Act in 1938, which required pharmaceutical manufacturers to provide scientific evidence of drug safety before marketing their products. The thalidomide tragedy later marked a pivotal moment in the evolution of pharmacovigilance. Introduced in 1957, thalidomide was widely prescribed as a seemingly harmless remedy for morning sickness and nausea.

Despite being tested on around 300 patients without reported toxicity, it became associated with congenital abnormalities, specifically phocomelia, resulting in severe birth defects in children born to women who had taken the medication during pregnancy. In 1962, following numerous reports of phocomelia cases, thalidomide was withdrawn from the market. That same year, the Kefauver-Harris amendment was passed, mandating scientific evidence of both efficacy and safety before drugs could undergo human testing. To consolidate existing data on adverse drug reactions (ADRs), the WHO established the Program for International Drug Monitoring in 1968. Initially launched as a pilot project in ten countries with existing national ADR reporting systems, this network has since expanded significantly as more countries developed their own systems.

Need Of Pharmacovigilance:

1. There may be a need to monitor the effects of drugs during the clinical trials and after it in market.
2. Adverse events can even happen during the clinical trials and after its launch in the market
3. Monitor the quality of drugs.
4. Identify the health risks involved in the administration of certain drugs. 5. Prevent harm to people. 6. Research the efficacy of drugs.

Scope Of Pharmacovigilance:

The field of Pharmacovigilance (PV) has evolved significantly since the 1972 WHO technical report, and it continues to be a dynamic clinical and scientific discipline. PV is crucial for addressing the challenges posed by the increasing variety and potency of pharmaceutical and biological products, including vaccines, which inherently carry risks of harm that can be unpredictable. The likelihood of adverse effects is reduced when medicines are utilized by well-informed healthcare professionals and patients who understand and share responsibility for their treatments. When new adverse effects or toxicities arise, especially those not previously associated with a medication, it is vital to analyze and communicate this information effectively to an audience capable of interpreting it. While substantial progress has been made in PV, further integration of this discipline into clinical practice and public policy is necessary. To meet regulatory PV obligations for marketed products, a pharmaceutical company in India must engage in activities such as collecting and promptly reporting serious unexpected adverse drug reactions (ADRs). A typical PV setup involves various personnel at different levels and an organizational structure designed to facilitate these processes.

Pharmacovigilance In Healthcare Emergency:

During the early waves of the pandemic, the lack of vaccines and effective treatments for COVID-19 prompted a rush to repurpose existing drugs approved for other conditions. Consequently, many drugs, such as hydroxychloroquine, ivermectin, and azithromycin, were used off-label for treating COVID-19 patients, despite the low quality of underlying scientific evidence, which was primarily based on in vitro studies. In this context, pharmacovigilance monitoring was essential for identifying the risks associated with off-label drug use, reinforcing the principle of "do no harm," especially when evidence of benefits was weak or absent. A notable example is azithromycin, a macrolide antibiotic frequently used for COVID-19 treatment. Its known risk of causing arrhythmias, particularly when combined with other COVID-19 treatments like hydroxychloroquine, prompted regulatory agencies to issue warnings against its use, except in cases of bacterial superinfection.

The expedited approval of drugs and vaccines during the COVID-19 pandemic highlighted the urgent need to gather safety data in post-marketing settings to identify and mitigate serious risks, ultimately ensuring patient safety. Another

important lesson from the pandemic is the significance of effective risk communication regarding drugs and vaccines to both healthcare providers and patients, facilitating informed therapeutic choices and appropriate usage. Conversely, ineffective communication can erode public trust in regulators and other stakeholders and may lead to adverse outcomes. An example of this is hydroxychloroquine, which received significant attention as a potential COVID-19 treatment. Despite unproven efficacy, it was promoted by influential figures, including former U.S. President Donald J. Trump. This resulted in a marked increase in purchases and online searches for hydroxychloroquine and chloroquine following his endorsements demonstrating how misleading information from powerful individuals can lead to inappropriate drug use and increase the risk of serious adverse reactions.

Database Networks For Post-Marketing Surveillance For Vaccines And Medicines:

The increased availability of large-scale distributed database networks offers new opportunities for monitoring the post-marketing safety of vaccines and medicines and generating real-world evidence to inform decision-making. To this end, in May 2008, the FDA launched the Sentinel Initiative, an infrastructure designed to analyze electronic healthcare data to evaluate the safety of approved medical products. To date, Sentinel has established one of the largest distributed database networks for assessing medical product safety, including the Sentinel System, which utilizes common data models and analytic tools to analyze existing real-world data, and the FDA-Catalyst, which employs routine queries and interactions with health plan members and providers. Pharmacoepidemiological studies that integrate multiple databases are particularly valuable for examining rare outcomes or exposures and for generating evidence across different countries, enhancing the strength and external validity of findings. Combining several claims databases can provide the statistical power necessary to explore the relationship between significant safety outcomes and specific drug exposures. An illustrative example is the Italian VALORE project, which demonstrates the potential of a distributed network of administrative databases for conducting post-marketing surveillance of biological drugs, including biosimilars, among Italian patients with immune-mediated inflammatory diseases.

One key takeaway from the COVID-19 pandemic is the significant potential of distributed networks of administrative databases to rapidly generate robust real-world evidence during public health emergencies. A case in point is the ITA-COVID19 network, an Italian multiregional initiative established to conduct pharmacoepidemiological studies evaluating the links between drugs, vaccines, and COVID-19 by connecting claims databases with COVID-19 registries . Other examples of distributed networks utilizing real-world data for COVID-19 research include Open SAFELY, an English analytics platform for electronic health record analysis , and the Observational Health Data Sciences and Informatics (OHDSI) program, which is an interdisciplinary collaboration focused on generating real-world evidence through large-scale analytics.

Artificial Intelligence In Pharmacovigilance:

The availability of healthcare data has significantly increased in recent years and is expected to grow further in the near future due to the widespread adoption of digital tools that collect patient-derived data. This vast amount of electronic data presents an opportunity to leverage artificial intelligence (AI) techniques to enhance drug safety assessment. Information extraction through natural language processing (NLP) and text mining techniques is becoming increasingly important in clinical research, enabling the

extraction of relevant insights from largely unstructured data sources. In pharmacovigilance, text mining and NLP can effectively gather information on adverse drug reactions (ADRs) and drug-drug interactions from various textual sources, aiding researchers and clinicians in monitoring drug safety . Currently, both public and private organizations are working on developing AI tools to automate the processing of ADRs.

AI and machine learning can also play a vital role in pharmacovigilance by:

1) automating tasks related to case report entry and processing,

2) identifying clusters of adverse events that may indicate underlying syndromes,

3) facilitating pharmacoepidemiological studies,

4) linking data through probabilistic matching within datasets, and

5) predicting and preventing adverse events using specific models based on real-world data.

Safety Monitoring Of Digital Therapeutics:

Digital therapeutics (DTx) represent one of the newest frontiers in medicine, defined as "technologies that deliver medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a wide range of diseases and disorders".

As the adoption of DTx increases in clinical practice, it is essential to implement effective post-marketing surveillance to quickly identify potential safety signals and establish the safety profiles of these technologies. While the side effects associated with DTx may generally be less severe and more manageable than those linked to conventional medications, adverse effects can still occur at rates higher than those observed in control groups during pivotal trials, necessitating careful post-marketing monitoring. Additionally, DTx enable the collection of vast amounts of post-marketing patient-level data, which can be used to reassess their safety and effectiveness in real-world settings. However, the rise in individual patient-related data raises concerns regarding data privacy and quality, underscoring the need for a legal framework that ensures both the protection of individual privacy and the transparent sharing of data for research purposes. By 2002, over 65 countries had established their own pharmacovigilance centers. The World Health Organization (WHO) coordinates membership for international drug monitoring through the WHO Collaborating Centre for International Drug Monitoring, commonly known as the Uppsala Monitoring Centre (UMC). Pharmacovigilance is now firmly grounded in sound scientific principles and is essential to effective clinical practice. However, the discipline must continue to evolve to meet public expectations and the challenges of contemporary public health. The Sixteenth World Health Assembly adopted resolution WHA 16.36, which emphasized the importance of promptly disseminating information about adverse drug reactions. This resolution ultimately led to the establishment of the WHO Pilot Research Project for International Drug Monitoring. The aim of this initiative was to create a system that could be applied internationally to detect previously unknown or poorly understood adverse effects of medicines.

Pharmacovigilance Of Advanced Therapy Medicinal Products:

Advanced therapy medicinal products (ATMPs) are medicines intended for human use that are based on gene, cell, or tissue engineering . ATMPs offer new possibilities to restore, correct, or modify physiological functions or facilitate medical diagnoses. Due to their innovative nature, these therapies often benefit from accelerated assessment and approval pathways, underscoring the importance of generating post-marketing evidence regarding their benefit-risk profiles.

However, uncertainties about the safety of new ATMPs cannot solely be attributed to regulatory processes. Since these therapies frequently target

rare diseases, pre-marketing evidence is often limited due to the inherent challenges of clinical trials, such as small sample sizes, reliance on surrogate endpoints, and single-arm study designs . Consequently, post-marketing studies are crucial for generating long-term safety evidence and addressing the knowledge gaps left by pre-marketing studies. Early detection of safety issues should occur throughout the development of ATMPs to mitigate risks when possible. In some instances, ATMPs are designed to be one-time treatments, making the sustainability of their efficacy a critical question that can only be addressed through long-term follow-up. The objectives of safety and efficacy monitoring will vary based on the specific characteristics of the product . For example, in the case of chimeric antigen receptor T-cell (CAR-T) therapies, routine risk minimization measures must be enhanced with additional strategies to address significant risks, such as cytokine release syndrome, infections, and serious neurological adverse reactions.

Ecopharmacovigilance:

Ecopharmacovigilance is defined as "the science and activities concerning the detection, assessment, understanding, and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, affecting both humans and other animal species" It is an increasingly important issue today, playing a crucial role in reducing the environmental risks associated with pharmaceutical pollutants. Pharmaceuticals are pervasive environmental contaminants, entering the environment through various pathways, including excretion by patients as parent compounds or active metabolites via wastewater systems, and discharges from manufacturers or hospitals .Numerous studies have documented the impacts of pharmaceutical pollution on diverse animal species, such as vultures and fish. The role of ecopharmacovigilance is becoming ever more critical in controlling and minimizing sources of pharmaceutical pollution by detecting, assessing, and preventing adverse effects linked to pharmaceuticals in the environment. Although the concentrations of pharmaceuticals detected in the environment are generally low (ranging from ng/L to μg/L), potential direct and indirect risks to humans still exist and require careful monitoring. For example, sex hormones can exert pharmacological effects at very low concentrations, and antibiotic exposure may contribute to bacterial resistance . Additionally, vulnerable populations such as pregnant women, children, and the elderly may be particularly susceptible to even low levels of medications. Addressing pharmaceutical pollution is thus a primary goal of modern pharmacovigilance.

At Frontiers in Drug Safety and Regulation, we are committed to promoting research in pharmacovigilance, pharmacoepidemiology, regulatory science, and public health. Our aim is to enhance regulatory sciences through patient-oriented approaches that tackle emerging drug safety issues.

Future Prospects:

As the future of pharmacovigilance (PV) expands, it is crucial to develop systems that can effectively detect new adverse drug reactions (ADRs) and implement regulatory actions to safeguard public health. There has been insufficient focus on generating information that aids healthcare professionals and patients in their decision-making processes. Collecting and communicating safety information is a key objective of PV, particularly through active surveillance methods. When creating new active post-marketing surveillance techniques, it is vital to gather complete and accurate data on every serious reported event. Although spontaneous reporting is valuable for generating signals, the relatively low number of reports for specific associations limits its ability to

identify patient characteristics and risk factors. PV methods must evolve to better describe which patients are at risk for developing ADRs, aligning with the increasing involvement of patients in drug safety.In the future, PV should focus on patients as key sources of information, alongside traditional sources like healthcare professionals. The Drug Controller General of India (DCGI) should act swiftly to enhance PV practices by integrating Good Pharmacovigilance Practices (GPP) into processes that ensure regulatory compliance and improve clinical trial safety and post-marketing surveillance. An effective PV system is essential for the careful use of medicines, benefiting healthcare professionals, regulatory authorities, pharmaceutical companies, and consumers alike.

Currently, post-marketing PV is a challenging and labor-intensive process for both the industry and regulatory agencies. The goal of PV is to efficiently receive and document information online, prioritizing new and significant safety issues. While non-serious events are screened routinely, they hold less priority compared to serious events. For instance, GlaxoSmithKline has implemented an innovative PV approach that combines traditional case-based methods with disproportionality and data visualization tools. This framework supports real-time review and tracking of safety issues, enhancing knowledge management.

Such innovative tools and processes can significantly advance PV by improving efficiency and analytical capabilities. A similar approach could be adopted by other pharmaceutical companies for the prompt detection and analysis of ADRs. Enhancing transparency and communication will strengthen consumer reporting, fostering greater consumer involvement in PV efforts.

CONCLUSION:

The field of pharmacovigilance is evolving rapidly in response to the increasing complexity of healthcare systems and the growing demand for patient safety. Current trends highlight the integration of advanced technologies, such as artificial intelligence and big data analytics, which enhance the detection and management of adverse drug reactions. Furthermore, the emphasis on real-world evidence and patient-centered approaches is reshaping how safety data is collected and analyzed. Looking ahead, the future of pharmacovigilance will likely involve greater collaboration among stakeholders, including regulatory bodies, healthcare professionals, and patients. As we move toward a more proactive and transparent pharmacovigilance framework, continuous adaptation and innovation will be essential to ensure the safety and efficacy of medications in an ever-changing landscape

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