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A REVIEW ON PHARMACOVIGILANCE AND DRUG SAFETY MEASURES

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ABSTRACT

Pharmacovigilance, or PV, is the process of continuously monitoring pharmaceuticals once they are put on the market in order to evaluate and enhance their safety profile. Increasing the number of adverse drug reactions (ADRs) that are spontaneously reported is the primary goal in order to collect a wide range of data. The World Health Organization (WHO) defined pharmacovigilance as the science and set of procedures concerning the identification, assessment, comprehension, and rejection of negative effects or problems associated with various drugs in nursing. A clinical test may involve an analysis study involving human subjects in order to address particular health questions. Carefully carried out clinical trials are the fastest and safest methods because they help individuals receive treatments that work and because they improve health. Pharmacovigilance, which provides information on the negative effects that the drug-using population typically experiences, is acknowledged to be essential to the sensible use of pharmaceuticals. Adverse drug reactions (ADRs) are becoming more and more common, and various methods, including scientific and administrative research, in-depth observation, impromptu reporting, and information studies, are being developed with the goal of enhancing pharmacovigilance. Because assessment procedures contain some subjective judgements, integrator reliability is frequently low. In summary, there is presently no well recognized mechanism for assessing casualties from ADRs.

INTRODUCTION[(1,2)]

According to the World Health Organisation (WHO), "Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effect or any other possible drug-related drawback, particular, long term and short term adverse effects of medicines" . Pharmakon (Greek for "drug") and vigilare (Latin for "to keep watch") are the origins of the term "Pharmacovigilance." . Pharmacovigilance is not a new concept in Asian countries; it has been practiced since 1998. .When Asian countries decided to join the Uppsala Centre for Adverse Event Monitoring. The spontaneous reporting of adverse drug reactions and adverse events is a critical tool for gathering safety data for early detection.

Before it can be marketed commercially, it must go through several stages of testing to ensure its safety and efficacy. However, clinical trials have several limitations, including the following: strict inclusion and exclusion criteria limit their use to a very select group of patients; special population groups such as children, pregnant women, and the mature population are not studied during the trials; and other factors causing drug reactions such as genetic factors, environmental factors, and drug-drug interactions may not have been studied during the clinical trials.

These adverse drug reactions (ADRs) not only increase patient suffering, but also morbidity and mortality, as well as a financial burden on society. In hospitalised patients, the overall incidence of ADRs is estimated to be 6.7% (0.1-0.85%).5. data show that in patients who have ADRs, the death rate is 19.18% higher and the length of hospital stay is 8.25% longer. Total medical costs for patients with ADRs increased by an average of 19.86%.

Drug safety has surged to the forefront of pharmaceutical concerns, taking precedence as the primary focus before any medication enters the market. Recognizing the limitations of clinical trials in fully assessing safety, it's now widely acknowledged that these trials alone cannot provide adequate safety information to protect public health. To address this, there are now stringent provisions in place to continually monitor drug safety after a product receives market authorization, mandated by regulatory bodies. Pharmacovigilance, which arose after the tragic thalidomide event in the 1960s, has become pivotal in mitigating drug safety oversights. Since then, substantial strides have been made in this arena, from spontaneous reporting systems to the contemporary implementation of risk management plans, all aimed at progressively enhancing drug safety.

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Despite efforts, adverse drug reactions (ADRs) remain inevitable, though some can be averted. The acquisition of new insights into novel and rare ADRs, especially those related to newly introduced medications, remains crucial to safeguard public health. Pharmacovigilance operates as an ongoing process, continuously monitoring drug safety while providing updated information and insights into ADRs. This information is indispensable for drug regulators, empowering them to make informed decisions concerning marketed drugs. The understanding that drugs are evaluated based on their benefit-risk ratio underscores the importance of these insights. Regulators are empowered to impose warnings, alter labels as restrictions, or ultimately withdraw drugs from the market based on this crucial information. Stakeholders, including drug regulators, maintain a constant vigilance over drug safety issues, illustrated by examples such as the recent withdrawal of rosiglitazone from the European market and the historical removal of well-known drugs like terfenadine, cisapride, phenylpropanolamine, refocoxib, and cerivastatin due to safety concerns. Therefore, the role of drug safety monitoring, encapsulated in pharmacovigilance, stands as an essential pillar in ensuring public health safety.

HISTORY OF PHARMACOVIGILANCE[3,4]

The thalidomide tragedy in the 1960s marked a pivotal moment in drug safety, prompting global initiatives. The 1893 Lancet publication on chloroform deaths also fueled concerns. Amendments to the US FDA Act in 1906 and 1962 addressed safety after sulphanilamide elixir fatalities and thalidomide, respectively. The UK's Medicines Act of 1968 and the World Health Organization's Program for International Drug Monitoring in 1968 further strengthened global drug safety efforts.

The Sequential Pharmacovigilance Developments

YEAR	DEVELOPMENTS
1747	The very first known clinical trials by James Lind proved the usefulness of lemon juice in preventing scurvy
1947	Death of more than 100 children due to toxicity of sulphanilamide
1950	Aplastic anaemia was reported due to Chloramphenicol toxicity
1961	Worldwide tragedy due to thalidomide toxicity
1963	16th World Health congregation recognizes significant to rapid action on Adverse Drug Reactions (ADRs).
1968	WHO research project for international drug monitoring on a pilot scale
1996	Global standards level clinical trials initiated in India
1997	India attached with WHO Adverse Drug Reaction Monitoring Program.
1998	Initiation of Pharmacovigilance in India
2002	67th National Pharmacovigilance Centre established in India.
2004-05	India launched National Pharmacovigilance Program
2005	The accomplishment of structured clinical trials in India.
2009-10	Pharmacovigilance Program (PvPI) started

FUNDAMENTALS OF PHARMACOVIGILANCE[5

Pharmacovigilance, crucial in public health legislation, focuses on detecting, assessing, and preventing adverse drug reactions. ADRs, causing 5% of EU hospital admissions and 200,000 deaths yearly, incur €80 billion in costs. The WHO's global drug monitoring program, initiated in 1968 with ten countries, now involves over 100, managing a database with 10 million adverse reaction reports.

ADVERSE DRUG REACTIONS (ADR)[6]

Adverse effects encompass all unwanted drug outcomes, avoiding mechanism assumptions, unlike toxic or side effects. Adverse drug reactions (ADRs) are unintended and unfavorable effects during clinical use, impacting patient quality of life. ADRs contribute to 5% of hospital admissions, with 10%-20% hospitalized individuals experiencing them. Timely identification and management are vital to mitigate harm.

CLASSIFICATION OF ADRs

Originally, adverse drug reactions (ADRs) were categorized as Type A (dose-dependent, foreseeable) and Type B (unpredictable). Later, Types C (chronic) and D (delayed) were added. Withdrawal (Type E) and therapy failure (Type F) followed. About 80% of hospital ADRs are Type A, often preventable. Common culprits include corticosteroids, antibiotics, and cardiovascular drugs in adults, and anti-infectives, respiratory drugs, and vaccines in children. For detailed management approaches, visit **DRUG SAFETY**

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SURVEILLANCE[7]

Efficient post-market drug surveillance is imperative to identify adverse drug events (ADEs) and safeguard public health. Traditional spontaneous reporting systems are passive and may miss up to 90% of serious ADEs. Leveraging electronic health records (EHRs) and advancing natural language processing (NLP) techniques offer a proactive and precise approach, crucial for large-scale drug safety monitoring.

RISK MANAGEMENT PLANS[8]

Proactive post-market surveillance advances with Risk Management Plans (RMPs), crucial in identifying and mitigating risks associated with medicinal products. The EU's RMP includes safety specifications and pharmacovigilance plans, evaluating the need for risk minimization activities. Plans are required for new substances, product modifications, new indications, or unforeseen risks, focusing on refining the benefit-risk ratio during post-authorization.

FUTURE PERSPECTIVES[8]

Recent regulatory advancements in pharmacovigilance require evaluation for their impact. While current focus is on detecting adverse drug reactions (ADRs), the field needs to prioritize generating information aiding healthcare decisions. Active surveillance, patient involvement, and innovative methodologies are crucial. Pharmacovigilance's evolution is evident, necessitating continued adaptation for robust drug safety and public health.

REGULATORY ASPECTS IN PHARMACOVIGILANCE[9]

Need Of Regulations in Pharmacovigilance

Regulatory bodies are becoming more forward-thinking in identifying possible safety concerns related to drugs on the market, demanding swift responsiveness from the pharmaceutical industry.

- Increased political and societal pressures coincide with faster communication methods.
- Legal actions resulting from inadequate pharmacovigilance can be profoundly damaging for all involved parties.
- Neglecting pharmacovigilance can result in the suspension or revocation of licenses in the United States.

NATIONAL PHARMACOVIGILANCE PROGRAM[10]

Initiated in November 2004 by the Central Drugs Standard Control Organization, India's National Pharmacovigilance Program aims to enhance drug safety by collecting and evaluating adverse drug reaction data. Operating through a three-tier framework and various centers, it facilitates swift regulatory actions to ensure public health.

Features of NPP

- Its immediate objective is to foster a culture of notification not only amongst doctors but also amongst other healthcare providers, viz., pharmacists and nurses.
- Although the drug regulators would be more interested in receiving information on adverse drug reactions of newly marketed drugs, the program allows reporting of common or non-serious adverse drug reactions of even well established drugs. This has been done to encourage every healthcare provider to start reporting adverse events.
- The reporting forms maintain patient confidentiality. Identification of notifier, however, is obligatory to allow for verification of information and discourage submission of spurious data.
- Now even practicing doctors and pharmacists can establish Peripheral Pharmacovigilance Centers.

GLOBAL PERSPECTIVES IN PHARMACOVIGILANCE[11]

WHO PROGRAM FOR INTERNATIONAL DRUG MONITORING

The WHO's International Programme for Adverse Reaction Monitoring, initiated three decades ago, aimed to detect rare adverse drug reactions globally. Evolving beyond its initial focus on managing a centralized database, the program, now known as pharmacovigilance, faces the challenge of adapting to the expanding concerns of diverse stakeholders in global drug safety monitoring.

TECHNOLOGICAL ADVANCEMENTS IN PHARMACOVIGILANCE[12]

Current Uses of Information Technology in Pharmacovigilance: Rule-Based Static Systems

Current pharmacovigilance (PV) systems rely on algorithmic approaches grounded in binary logic to manage safety data. These algorithms, managed by users, employ consistent and objective expert knowledge in a standardized manner, ensuring familiarity and comprehension of the outcomes of data processing. The European Good Pharmacovigilance Practice Annex 1 defines five (5) domains within PV systems, briefly outlined below:

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• **Quality (management) system (QMS) for the PV system**: The organizational structure, responsibilities, procedures, processes, and resources of the PV system as well as appropriate resource management, compliance management, and record management. The QMS is part of the PV system.
• **Risk management system**: A set of PV activities and interventions designed to identify, characterize, prevent, or minimize risks relating to a medicinal product, including the assessment of the efectiveness of those activities and interventions .
• **Management of ICSRs**: Collection, collation, processing, and assessment of safety data to standardize the format and content of a relational database used for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specifc point of time
• **Aggregate reporting**: Periodic reports summarizing safety data received over a fixed-term for a specifed medicinal product, sometimes including a detailed comparison with the cumulative safety data for the product.
• **Signal management**: A set of activities performed to determine whether, based on an examination of ICSRs, aggregated data from active surveillance systems or studies, scientifc literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications, and tracking

Artificial Intelligence (AI)-Informed Static Systems[13,14]:
AI in pharmacovigilance streamlines processes, reducing human error and enhancing efficiency in ICSRs, aggregate reporting, risk management, signal management, and QMS.

DISCUSSION
Pharmacovigilance, a linchpin in drug safety, monitors and prevents adverse reactions throughout a drug's lifecycle. Evolving from traditional methods to AI and machine learning, it detects unforeseen effects, informs regulations, and ensures real-time surveillance. With a focus on continuous improvement, it fosters patient-centric care, optimizing the benefit-risk balance in a dynamic healthcare landscape.

CONCLUSION
Pharmacovigilance is a crucial aspect of modern healthcare, adapting to cutting-edge methods like AI and big data for real-time drug safety monitoring. Beyond signal detection, it provides personalized insights, optimizing treatment decisions. Transparent communication of risks enhances public trust, while its role in regulatory decisions ensures the highest patient care standards. In an evolving healthcare landscape, pharmacovigilance's commitment to innovation and patient-centricity safeguards lives, epitomizing an ethical ethos in medicine.

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