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PHARMACOVIGILANCE IN INDIA: PAST, PRESENT, AND FUTURE PERSPECTIVE

Ashwini R. Tamkhane* B. Pharmacy Student ClinoSol Research*Corresponding Author

Allada Shifali Rani Msc Microbiology Student ClinoSol Research

Gyansudha Gawali BDS Student ClinoSol Research

ABSTRACT Its start a decade ago, pharmacovigilance (PV) experienced tremendous development. There have been significant attempts in recent years to transform the current pharmacovigilance systems to meet future expectations. Adverse drug reactions (ADRs) are increasing in frequency, severity, and complexity as novel medication therapies are coming to market more quickly as a result of better laws and regulations. India is the second most popular nation in the world, with around 1 billion active and prospective consumers of pharmaceuticals. Despite being a member of the Uppsala Monitoring Centre, our nation has almost little commitment to the database. This problem is brought on by the inadequate ADR (adverse drug reaction) monitoring system and lack of knowledge among pharmacy associates and medical professionals. The primary objectives of the PV program are patient care, patient safety, and monitoring of negative medication reactions. There is a need for additional clinical preliminary exams and clinical assessments in India to accurately practice PV. A fully functional PV system is essential for the safe and responsible administration of medicines. This review gives a systematic review of pharmacovigilance in India from its origin to its current scenario and also discusses the various strategies and proposals to build, maintain and implement a robust pharmacovigilance system for India in coming years.

KEYWORDS : Adverse drug reaction, central drugs standard control organization, Uppsala monitoring center, world health organization, pharmacovigilance program in India

Introduction

No drug is safe! Any drug, no matter how common its clinical uses, has the potential to cause harm. Pharmacovigilance (PV) is the branch of pharmacological science, that deals with the collection, assessment, monitoring, and prevention of adverse effects of pharmaceutical products, particularly long-term and short-term adverse effects of medicines. The etymological origin for Pharmacovigilance is pharmacon = drug in the Greek language, vigilare = to keep watch in Latin and as per WHO. Pharmacovigilance is defined as the science and activities, connecting to the finding, evaluation, understanding, and prevention of adverse effects or any other drug-related problem. As such Pharmacovigilance heavily focuses on adverse drug reactions or ADRs, which are defined as any response to a drug that is noxious and unintended, including lack of efficacy. [1,2] before a product is marketed, the experience of its safety and efficacy is limited by the patient numbers and duration of trial as well as by the highly controlled condition in which clinical trials are conducted.[2]

WHO outlines the science and practices linked with the detection, evaluation, comprehension, and prevention of unintended effects or any medication-related concern. In 2010, 134 nations participated in the WHO's Pharmacovigilance initiative, which improved coordination between national and global medication monitoring. In 1986, India started to establish centers for monitoring adverse drug reactions. At first, it had more than ten provincial centers.[3]

To regulate the ADR system in this country, six territorial locations (Kolkata, New Delhi, Mumbai, Lucknow, Pondicherry, and Chandigarh) were hoisted at the arrangement. Only New Delhi and Mumbai actively report ADRs, with reports from other centers being unrestricted and poor. There are 22 AMCs throughout the nation at the moment. The number has increased to almost one hundred and fifty which has been circulated in four territories. [4,5]

Roots of Pharmacovigilance

After an incident in 1937, a new development in this sector was only made [1]. Around 105 children and 71 adults were discovered dead that year after consuming syrup containing diethyl glycerol and sulphonamide, which was responsible for their deaths. Since 1932, sulphonamide has been used to treat streptococcal infections. It was diluted as syrup and a solvent called diethyl glycerol was added.[5] Since 1932, sulfanilamide (Prontosil), a medication used to treat streptococcal infections, has been available as a syrup that contains the solvent diethylene glycol. Its flavor and odor were assessed, but its safety was not examined before it was marketed. Due to this tragedy, the American Congress passed the Food, Drug, and Cosmetic Act in 1938, requiring pharmaceutical companies to provide scientific proof of the product's safety before releasing them for sale. The thalidomide disaster marks an important turning point in the history of pharmacovigilance [5,6]. Thalidomide, safe medication for treating nausea and morning sickness, was first released in 1957. About 300 patients were evaluated, and there was no toxicity. It was soon discovered that it was connected to the congenital disorder phocomelia, which led to serious birth abnormalities in the offspring of pregnant women who had been administered this medication. It was abandoned in 1962 as a result of reports of multiple phocomelia cases [3,5]. The Kefauver-Harris amendment, which demands scientific evidence of efficacy and safety before drug experiments in humans, was approved that same year. The WHO's Programmed for International Drug Monitoring was established in 1968 as a way to combine the data already available on adverse drug reactions (ADRs). The network, which was initially a trial project in 10 nations with established national reporting systems for adverse drug reactions, has subsequently greatly grown as more nations globally established national pharmacovigilance centers for recording adverse drug reactions. Currently, 170 nations take part in the initiative, which is run by WHO and its collaborating center in Uppsala, Sweden. The worldwide ADR database, Vigibase, is kept up to date by the cooperating center. Currently, there are over four million ADR reports in the database. [1, 5]

Following are chronological sequences of how the network, which was initially a trial project in 10 nations with established national reporting procedures for ADRs, has grown dramatically as other nations around the world have evolved.

- 1937: More than 100 people died as a result of renal failure after sulphonamide was dissolved in diethylene glycol in the Sulphanilamide catastrophe.
- 1938: preclinical toxicity testing, as well as the premarketing clinical research authorized by the FDA.
- 1950: Chloramphenicol use resulting in aplastic anemia.
- 1960: The FDA launched a program for hospital-based drug monitoring.
- 1961: Thalidomide disaster.
- 1963: The 16th World Health Assembly highlighted the need for quick ADR action.[1]

History of pharmacovigilance in India

The concept of PV originated in the past because Vagbhatta, a

specialist who tended to unfavorable occasions, reason, and deferred ADRs to Ayurvedic Drugs' around 500 AD, had warned that appropriately witnessed, improperly coordinated medicine is somewhat of a poisonous substance in the hour of Charaka Samhita in 700 BC. Since the first attempt was made in 1989, there have been countless reports of adverse drug reactions (ADRs) from the Indian subcontinent throughout the history of modern medicine, but there has never been a systematic effort to track ADRs.[3,5,8]

In 1986, a formal Adverse Drug Reaction (ADR) including 12 provincial locations, each accounting for a population of 50 million people, was suggested. This proposal laid the groundwork for what is now known as India's Pharmacovigilance framework. However, not much changed until 1997, when India joined the WHO's ADR Monitoring Program in Uppsala, Sweden, ten years after the event. The Uppsala Monitoring Centre (UMC) was established to maintain a global data set of reports of suspected ADRs. Six centers were established in India to address this, namely in New Delhi, Lucknow, Chandigarh, Mumbai, Pondicherry, and Kolkata. However, only the National Pharmacovigilance Center at AIIMS, New Delhi, and two WHO-monitored centers in Mumbai (KEM Hospital and JLN Emergency clinic) were active among these six centers, and as a result, unrestricted announcing of ADRs was inadequate. [3,11]

The monitoring centers were seen as temporary and faced severe demands since appropriate levels of subsidies were not made available. The Indian government realized that ADR checking needed to be improved of India filed a request for financing to the World Bank. The National Pharmacovigilance Program (NPVP) was launched in November 2004 after the World Bank supported the idea with a long-term award of US$0.1 million each year. The National Pharmacovigilance Advisory Committee (CDSCO) located in New Delhi, monitored the NPVP. Two zonal centers, the South-West Zonal Center (located in the Department of Clinical Pharmacology at Seth GS Medical College and KEM Hospital in Mumbai) and the North-East Zonal Center (located in the Department of Pharmacology at AIIMS in New Delhi), gathered data from across the nation and sent it to the Committee in the same way that the UMC in Sweden.[13]

Current Scenario of Pharmacovigilance in India

India is a huge nation with over 6,000 licensed medicine producers and over 60,000 branded formulations. India ranks as the fourth-largest pharmaceutical manufacturer in the world and is quickly becoming a center for clinical trials. To safeguard the Indian people from possible harm that some of the new pharmaceuticals may cause, the pharmacovigilance system must be improved as a result of the numerous new drugs being released in the nation. In the past, there was not an immediate requirement for the government to set up a robust pharmacovigilance system of its own, thus Indian regulatory bodies and pharmaceutical corporations depended on their safety evaluations on experiences obtained from long-term medication usage in the Western markets. However, the time between a drug's release to the market and its subsequent availability in India has significantly decreased recently, making it impossible to get crucial long term safety data [3,14,15]. Additionally, drug companies based in India now have a greater ability to conduct their research, which has increased their capacity to create and market new medications. As a result, it is more crucial than ever to create adequate internal pharmacovigilance standards to identify adverse drug reactions. Additionally, Indian-based pharmaceutical companies now have more freedom to conduct their research, which has improved their ability to develop and distribute new drugs [16].

The Ministry of Health and Family Welfare (MHW), the Indian Council of Medical Research (ICMR), the Medical Council of India (MCI), the Pharmacy Council, the Nursing Council, the Dental Council, Pharmaceutical Companies, Consumer Associations, Non-governmental Organizations (NGOs), and Patient Groups should be invited to a high-level discussion to inform them of the plans the Drug Control General of India (DCGI) has to enhance and develop a strong system. Add qualified scientific and medical assessors for pharmacovigilance to the DCGI office to strengthen it [16,17]. Officials working in the DCGI's pharmacovigilance department as well as at the peripheral, regional, and zonal centers should get intensive training in all facets of pharmacovigilance. Training sessions should be organized twice a year for this to be a continuous activity. The creation of a single, uniform adverse event reporting form for the whole nation [17,18].

It is necessary to establish a common adverse event reporting form that can be utilized by the National Pharmacovigilance Centers, teaching hospitals, registered hospitals (both public and private), Drug Information Centers, and pharmacies nationwide. All primary healthcare centers (PHCs) in rural regions, as well as all active general practitioners and doctors, should have access to it. Building a post-marketing and clinical trial database. From the date of the first registration of the clinical trial in India, ADRs for signal detection and access to all pertinent data from various stakeholders' entire complete data shall be made accessible to the DCGI and to the various stakeholders [18,19].

This information should adhere to the rules for unified standards of reporting trials, including the product's overall benefit-risk profile. Information about all adverse events (AEs) and adverse drug effects (ADRs) per study arm should be systematically included, along with a detailed description of cases with previously unknown AEs, ADRs, and the reasons for study withdrawals. For drugs already on the market, the type and frequency of all adverse events (serious and non-serious) should be submitted in periodic reports in accordance with current standards of safety reporting as outlined in Schedule (SPCs) [1, 3, 19].

Record every new medication indication by keeping a consistent database for each pharmaceutical firm. Regulatory agencies and pharmaceutical companies should keep a list of every new drug indication in the database. There has to be stricter oversight of any new concerns. Pharmaceutical companies in these situations should schedule meetings with the DCGI to discuss their risk management plan (RMP) for the safety issues in question and how they would put in place efficient strategies to mitigate the Education and training of medical students, pharmacists, and nurses in the area of pharmacovigilance [19,20,].

Several courses are offered by different organizations that concentrate on clinical research, but as of now, none are pertinent to pharmacovigilance in the nation. The MCI and other stakeholders should include a pharmacovigilance curriculum in the pharmacology and medical curricula so that doctors may receive the required theoretical and practical training. In a similar vein, pharmacovigilance training should be provided to nurses and pharmacists so that they can identify adverse drug reactions (ADRs) and foster a culture of reporting ADRs in the future. Unique program for pharmacovigilance awareness and a training plan (including both online and in-person instruction) [3,21,22].

These are intended for pharmaceutical companies with a focus on research and development (R and D), particularly those engaged in new drug development, as well as for the medical community, pharmacists, and chemist-druggist trades, as well as patients, to be vigilant in spotting ADRs and reporting them to the Indian regulatory agencies, who will then investigate and take prompt corrective action. As information technology (IT) advances, new options for national and international collaborations that can improve post-marketing monitoring programmes and promote medication safety have emerged [23]. These collaborations can be made with pharmacovigilance groups to improve drug safety. An illustration of an international partnership to create a uniform post-marketing surveillance database is the Uppsala Monitoring Center (UMC). The approach depends on national drug monitoring institutes in 80 different nations exchanging data on adverse reactions. Through the internet, the data is quickly and securely sent, saved, and retrieved. [23,24]

Over four million entries with several data fields are included in the UMC database. With the assistance of knowledgeable commercial companies, a comparable database may be created for the DCGI using the safety information obtained from clinical trials and post-marketing surveillance. A core group of specialists will need to be established to establish a network of pharmacovigilance and pharmacoepidemiologists in India. This group will include representatives from multinational corporations (MNCs), Indian pharmaceutical businesses, and staff from the regulatory body (DCGI). Collaboration with the IT industry to create an effective pharmacovigilance system for India Software tools have been created that may be utilized for data collecting and analysis, trend analysis of drug consumption across a range of disease areas, compliance, prescription mistakes, and drug interactions that result in adverse drug reactions [25,26].

Strategies and proposal: The way forward in India

The discipline of pharmacovigilance has achieved an amazing progress in the recent decade since its beginning. In recent years, significant attempts have been made to revolutionize existing pharmacovigilance systems to satisfy future expectations. As the possibilities for the future improve, PV systems must be capable of detecting new ADRs and taking regulatory steps to protect public health. It is critical to design and implement systems for evaluating and monitoring the safety of medications in clinical use to avoid or limit harm to patients and promote public health. However, there are just too many pressing challenges hurting the healthcare system these days [27, 28]. Web-based sales and information, globalization, broader safety concerns, public health versus pharmaceutical industry economic growth, monitoring of established products, developing and emerging drugs, attitudes and perceptions to benefit and harm, outcomes and impact, and other related issues are some of the major challenges. It is more critical than ever to raise knowledge of PV and communicate this information from diagnosis to signal to control overall adverse medication responses, which has become one of PV's primary aims [2,29].

The collection and dissemination of this data is a key objective for PV. It's important to know the safety of medication active surveillance. When creating new active post-marketing monitoring techniques, it's critical to bear in mind how crucial it is to gather comprehensive and correct information on every Serious reported occurrence. However, due to the relatively small number of reports obtained for a given relationship, spontaneous reporting is less effective at detecting patient features and risk factors. PV techniques must also be able to identify whether patients are susceptible to experiencing a negative medication response (ADR). The PV strategy would be in line with the rising patient participation in medication safety as a source of knowledge [3,4].

The PV could be used to pinpoint specific risk factors for the development of certain ADRs. In addition to the more conventional groups, including the health professionals, PV must now focus on the patients as a source of information. Now is the time for the DCGI to strengthen PV to incorporate Good Pharmacovigilance Practice (GPP) into the processes and procedures, assist assure regulatory compliance, and improve clinical trial safety and post-marketing surveillance. If medications are to be used carefully, a well-functioning PV system is necessary. It will help consumers, pharmaceutical businesses, regulatory agencies, and healthcare professionals. It aids in the risk assessment of pharmaceutical products by pharmaceutical corporations. Post-marketing PV is now a difficult and time-consuming procedure for regulatory bodies as well as the entire industry [11,14].

A well-functioning pharmacovigilance system is essential if medications are to be used safely. All stakeholders, including healthcare professionals, regulatory agencies, pharmaceutical corporations, and consumers, will benefit from it. It helps pharmaceutical businesses create and implement comprehensive threat management plans to safeguard their medications in perilous circumstances, as well as continually monitor their products for threats.

The capability of the following suggestions is as follows:
1) Constructing and maintaining a strong pharmacovigilance system.
2) Making Pharmacovigilance announcements required and sporadically providing Pharmacovigilance investigations without recommendations.
3) Verifiable dialogues with various groups of the workforce.
4) Strengthening of the DCGI office with ready pharmacovigilance logical and clinical assessors.
5) Establishing a single, universally accepted, country-explicit, hostile event announcement structure.
6) Making a specific clinical pre and post-showcasing information base for SAEs/SUSARs and ADRs to accept all understanding information from various partners and recognize signals.
7) Training and instruction in the field of pharmacovigilance for medical students, pharmacists, and nurses [3,5].

The PV may contribute to certain risk factors that result in the occurrence of some ADRs. Later, PV must concentrate on using people as a source of information in addition to more conventional groups like health professionals. To implement Good Pharmacovigilance Practice (GPP) into the cycles and tactics to assist ensure administrative consistency, upgrade clinical preliminary security, and enhance post-advertising observation, the DCGI should take action quickly to improve PV [22,28].

Conclusion

India has 6, 24,000 beds across 15,000 hospitals and more than 500000 certified doctors. India is the world's fourth-largest maker of pharmaceuticals. The nation has made a name for itself as a prominent center for clinical trials. It is growing in significance as a global center for clinical trials. In our nation, several new pharmaceuticals are being introduced. As a result, the country needs a robust pharmacovigilance system to protect the general public from any possible harm that any of these new pharmaceuticals may cause. In India, pharmacovigilance is still a new topic and has not progressed much. India performs at a pharmacovigilance rate of less than 1%, compared to a global average of 5%. This is due to a lack of preparation and general ignorance of the topic. The PvPI has grown and developed into a vital component of India's whole drug system over its eight-year existence up to this point. It has helped in bringing drug-related incidents and suggested changes to various therapies that are geared toward the patients' benefit to the attention of the local medical services community as well as the general populace.

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