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Pharmacovigilance: Present Scenario and Future Goals

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ABSTRACT

Melton Pharmacovigilance is the science and activity relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. Pharmacovigilance basically targets safety of medicine. Pharmacists have crucial role in health systems to maintain the rational and safe use of medicine for they are drug experts who are specifically trained in this field. The perspective of pharmacy students on pharmacovigilance and ADR reporting has also been discussed with an aim to highlight the need to improve content related to ADR reporting and pharmacovigilance in undergraduate pharmacy curriculum. Globally, although the role of pharmacists within national pharmacovigilance systems varies, it is very well recognized. Incorporation of ADR reporting concepts in education curriculum, training of pharmacists and voluntary participation of pharmacists in ADR reporting is very crucial in achieving the safety goals and safeguarding public health. Also, these knowledge gaps can be fulfilled through continuous professional development programs and reinforcing theoretical and practical knowledge in undergraduate pharmacy curriculums. Without adequately identifying and fulfilling training needs of pharmacists and other health care professionals, the efficiency of national pharmacovigilance systems is unlikely to improve which may compromise patient's safety.

Keywords: Prevention; Monitoring; Pharmacists; ADR; Safety; Medicine

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Abbreviations: Computerized Provider Order Entry (CPOE); Clinical Decision Support (CDS); Drug-Drug Interactions (DDIs); Healthcare Professionals (HCPs); Hypersensitivity Drug Reactions (HDRs); European Medicines Agency (EMA); Fatal Adverse Drug Reactions (FADR); Medicines Use Review (MUR); Uppsala Monitoring Centre (UMC)

Purpose of the study: Discussion and projection of present situation analysis and future demand of pharmacovigilance. The pharmacists have a vital role to play which is thoroughly discussed.

Methodology: Research conducted a year-round comprehensive literature search, which included technical newsletters, newspapers journals, and many other sources. The present study was started from the beginning of 2018. PubMed, ALTAVISTA, Embase, Scopus, Web of Science, and the Cochrane Central Register of was thoroughly searched. The keywords were used to search for different publishers' journals like Elsevier, Springer, Willey Online Library, Wolters Kluwer were extensively followed. Medicine and technical experts, pharma company representatives, hospital nurses and chemists were given their valuable suggestions. Projections were based on estimates such as drug end users, providers or prescribers, general knowledge of rational use, consequence and types of different incidences of ADR and non-compliance, their managements or overlooking. Studies regarding inclusion and information sources of pharmacovigilance were given priorities. Several factors that influence medication taking behavior, non-compliance, ADR reporting by pharmacists were collectively analyzed and added to the article. Issues regarding economic and cultural barriers were found to be different from subcontinents, countries and even states. Most important features of pharmacist's role in therapeutic intervention were added afterwards to maintain a logical sequence. Drug factors, environmental factors and provider-patient interaction followed by pharmacist's role in handling patients and to

change or correction of medication counseling, dispensing, monitoring was added to reveal their effect on patient compliance which is the ultimate goal of meeting therapeutic guidelines. Many studies found regarding pharmacists' role in therapeutic cost minimization, role in hospital and other healthcare settings, disease prevention and lifestyle management found to be not within the scope of this article.

Findings: Pharmacists are integral part of healthcare management system and importance of their role play is not after doctors and nurses. Any future role for the pharmacist in counseling, monitoring and vigilance could be addressed as part of a formalized, strategic approach to creating an integrated healthcare team, with attention to further improvement of pharmacovigilance in any country, community or a healthcare setting.

Research limitations: Research has the major limitation with dealing too many information on pharmacovigilance worldwide. Only important aspect of expanded role of pharmacists, present situation of vigilance in different countries and a few future prospect, demand and necessities of pharmacists in meeting those emerging demands are discussed.

Practical Implication: The soul of this article was to detail about present situation and future demands of pharmacovigilance. Along with students, researchers and professionals of different background and disciplines, e.g. Pharmacists, marketers, doctors, nurses, hospital authorities, public representatives, policy makers and regulatory authorities have to acquire much from this article.

Social Implication: The article should contribute an integrated guideline for patient compliance, demand pharmacovigilance and last but not the least a silvery lining to better healthcare situation in near future.

Introduction

WHO defined pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of

adverse effects or any other drug-related problem". It is a very significant and inseparable part of clinical research. Both clinical trials safety and post-marketing pharmacovigilance (popularly known as Post marketing studies or Phase IV clinical trials) are critical throughout the product life cycle. With a reasonably high number of recent high-profile drug withdrawals, both the pharmaceutical industry as well as various regulatory agencies across the globe have raised the bar. Early detection of signals from the post-marketing surveillance studies and clinical trials in early phases have now been adapted by major pharmaceutical companies in order to identify the risks associated with their medicinal product/s as early as possible. An ADR is defined by the WHO as "a noxious, unintended effect of a drug that occurs in doses normally used in humans for the diagnosis, prophylaxis and treatment of disease". The occurrences of ADRs depend on the age, sex, genetic, polypharmacy, dose accuracy, and environmental and other internal factors like disease conditions. ADRs commonly reported in due to known or unknown pharmacological features, poor product quality (e.g., spurious, adulterated, misbranded, counterfeit, substandard), medication errors in prescribing, preparing, administering, or taking the medicine which requires hospitalization, causing significant disability/incapacity, sometimes life threatening and also death reported.

Inclusion

Pharmacovigilance is a process which includes:

- The monitoring of use of medicinal products in everyday clinical practice, so as to be able to identify previously unidentified adverse reactions or a change in the nature of adverse reactions.
- Risk-benefit assessment of medicinal products, which helps to decide what action, if necessary, is essential for a safer use of medicinal products.
- Provision of information to healthcare professionals as well as to patients in

order to improve the safe and effective use of medicinal products.

Sources of information in pharmacovigilance

Pharmacovigilance uses information from many sources:

- Spontaneous reporting of adverse reactions from healthcare professionals (link to adverse reactions)
- Clinical trials and epidemiological studies
- Published global medical literature
- Pharmaceutical companies
- Healthcare and population statistics
- Information on the consumption of medicinal products

Types and Prevalence of ADRs

Adverse drug reactions (ADRs) in hospitalized patients can be divided into two categories: those that are the cause of hospital admission, and those that occur during hospitalization. There are limited data on ADRs, especially regarding the reactions that occur after admission. It is estimated that ADRs occur in 10% of the general population and 10 to 20% of in-patients, more than 15% of these ADRs can be fatal [1], [2]. Approximately 15 to 20% of ADRs correspond to HDRs, which are induced by exposure to a drug in a dose that is usually tolerated by healthy individuals, and the reactions are characterized by objective symptoms that can be reproduced following subsequent re-exposure [2]. ADRs represent an important cause of morbidity and are thought to cause between 10% and 30% of all hospital admissions in older patients [3]. In USA, more than 90% of adults aged 65 year and older use one medication per week and 10%-25% experience an adverse drug reaction [4]. These ADRs are responsible for 3-7% of hospital admissions. The prevalence of ADRs was more in female patients as compared to men. ADRs mostly occurred in the age group of 41-50 years [5].

The Value of Patient Reporting

Patient reporting adds new information, and perspective about ADRs in a way otherwise unavailable. This can contribute to better decision-making processes in regulatory activities in the EU, there were 48,782 patient reports in 2015, representing an increase of 30% on 2014 [6]. Most patients were not aware of reporting systems and others were confused about reporting. Patients were mainly motivated to make their ADRs known to prevent similar suffering in other patients. By increasing patient familiarity and providing clear reporting processes, reporting systems could better achieve patient reporting of ADRs. The WHO monitors spontaneous ADR reporting in the majority of countries. A common problem is under-reporting. It is estimated that only 5–10% of ADRs are reported. Although there is no estimate of patient reporting, 95% of HCPs do not report ADRs. In 1976, a British physician, Inman, was the first to publish reasons for under-reporting by HCPs, including:

- Complacency (believing that serious ADRs are well documented when the drug is released on the market)
- Fear of being involved in a lawsuit
- Guilt for having been responsible for damage observed in a patient
- Ambition to publish a case series or financial benefit
- Lack of awareness of the notification process
- Insecurity about reporting suspicions of an ADR
- Indifference [7]

The Value of Healthcare Professionals' Reporting

The information collected during the premarketing phase is incomplete with regard to adverse drug reactions and this is mainly because

- Patients used in clinical trials are limited in number and are not representative to the public at large. In addition, the conditions of use of medicines differ from

those in clinical practice and the duration is limited.

- Information about rare but serious adverse reactions, chronic toxicity, and use in special groups (such as children, the elderly, or pregnant women) or drug interactions is often incomplete.

Therefore, post-marketing surveillance is important to permit detection of less common but sometimes very serious ADRs. It is important to permit detection of less common, but sometimes very serious ADRs. Health professionals worldwide should report on ADRs as it can save lives of their patients and others [8]. Signal detection is important to identify the drug related adverse effects. However, the number of reports sent to national pharmacovigilance centers is also important as well as the quality of reports. The quality of reports is definitely superior when they are filled by health professionals who have pharmacology knowledge, i.e. pharmacists, doctors, nurses, physician assistants, dentists etc. It will be even better if it can be documented and retrieved from pharmacy information systems.

Factors of ADR Reporting

ADRs have emerged as a major clinical and public health problem responsible for approximately 5 to 35% of hospital admissions in both developed and developing countries. In the United States and Europe, ADRs are among the top ten causes of mortality as well as increasing the cost of care. Prompt reporting of ADRs to drug regulatory bodies is an important drug safety measure but under-reporting is a major challenge even in developed countries with adequate human and material resources to tackle the problem [9]. Factors that may contribute to underreporting among HCPs include knowledge, negative attitudes, lack of time and motivation. Lack of standardized reporting processes and gaps in healthcare information systems also contribute to underreporting [10]. Providers documented adverse drug events in charts to support continuity of care but never reported them to

external agencies. Providers faced time constraints, and reporting would have required duplication of documentation [11]. Surveys of health care practitioners in acute hospitals have found that nurses are more likely to report incidents than doctors and that there are various reasons for staff not reporting, including not knowing how to report incidents, time constraints, uncertainty about what to report, the expectation of blame or punishment, and a perception that reporting incidents does not result in improvements [12].

Biological Medicines Pose Specific Challenges for Pharmacovigilance

A recent guideline published by the EMA highlights four key considerations for the pharmacovigilance of biologicals; namely immunogenicity, manufacturing variability, stability/cold chain requirements and product traceability. Biological medicines are inherently variable and although different batches of the same biological medicine are not identical, the quality of each batch is tightly controlled to ensure the safety and efficacy of the medicine. However, necessary manufacturing process changes can impact quality attributes of the biological and this can occur unbeknownst to healthcare professionals and patients. In rare instances, these changes can have unforeseen effects on the immunogenicity of a product. Biological medicines including biosimilars are becoming increasingly available. Biosimilars are distinct from the generics of chemical medicines as, owing to the complexities of biological substances and their manufacturing processes, biosimilars are not completely identical to the original medicine on which they are based (reference medicine). Similarity to the reference medicine is demonstrated through a rigorous comparability exercise conducted at the quality, pre-clinical and clinical levels. All newly approved biological medicines, including biosimilars, are subject to additional monitoring for a period of 5 years after approval [10].

Medical and Economical Burden of ADRs

Medical burden of FADRs is significant. The most important concerns are prescribed medicines, omission of necessary treatment, failure to monitor treatment and poor systems. These were related to defects in education or training, lack of clear guidelines or protocols and failure to implement existing guidelines, among other reasons [13]. An estimated 106,000 deaths reported between 1966 and 1996 in US. However, it is estimated that only 6% of ADRs are reported [2]. And 50%- 70% are deemed preventable. An estimated 197,000 deaths per year in the European Union are caused by ADRs and the total cost to society of ADRs in the EU is €79 billion. ADRs represent the fifth most common cause of death in hospital setting [14]. In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes [15]. Between 1976 and 2007, 28 drugs were withdrawn from the US market for safety reasons [16]. Mortality rates due to ADRs are estimated from 0.1-2.9%. A retrospective eight-year (1999-2006) study conducted in the US of >2 million deaths revealed that 2341 deaths (0.1 per 100,000) were ADR-related deaths. In 2005, drugs were the leading cause of death estimated at 739, 936 per year [17]. The estimated total financial cost of \$17.88 billion represents 1.55% of Australian gross domestic product [18].

Pharmacovigilance in Healthcare Education

Healthcare professionals have little awareness of pharmacovigilance and ADR reporting, and only few educational interventions had durable effects on this awareness. Future healthcare providers should therefore acquire an adequate set of pharmacovigilance competencies to rationally prescribe, distribute, and monitor drugs. Foreseeing, recognizing, managing, and reporting adverse drug reactions (ADRs) are an important part of rational and safe prescribing and are integrated into multiple steps of the WHO-six-step Guide to Good Prescribing [19]. Numerous studies have expressed concern about the lack of healthcare professional

competencies in pharmacovigilance [20, 21]. This lack of undergraduate education and training in pharmacovigilance is consistent with the low level of knowledge, skills, and actions seen not only in physicians but also in practicing pharmacists, dentists, and nurses [22-24]. Unfamiliarity with pharmacovigilance, a low level of ADR-reporting skills, a lack of knowledge combined with negative attitudes like ignorance, fear legal liability, and lack of importance are thought to be related to the current inadequate response to many ADRs [25-28]. Several interventions (implementing protocols, educational workshops, or repeated emailing or telephone calls) have been implemented in an attempt to improve the competence of healthcare professionals [29-32], but these interventions are costly or fail to produce clinically relevant and long-term effects [23].

Pharmacovigilance in Pharmaceutical Industries

The aims of pharmacovigilance within the industry are essentially the same as those of regulatory agencies; that is to protect patients from unnecessary harm by identifying previously unrecognized drug hazards, elucidating predisposing factors, refuting false safety signals and quantifying risk in relation to benefit. Although the perspectives of companies and the regulatory agencies may be different, they now work more and more closely together and share information [33].

Worldwide Monitoring of Pharmacovigilance

In 2002, more than 65 countries have their own pharmacovigilance centers. Membership of the WHO for International Drug Monitoring is coordinated by the WHO Collaborating Centre for International Drug Monitoring, known as the UMC. Pharmacovigilance is now firmly based on sound scientific principles and is integral to effective clinical practice. The discipline needs to develop further to meet public expectations and the demands of modern public health. A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring.

- A. **The Quality Assurance and Safety:** The team is a part of the Department of Essential Drugs and Medicines Policy, within the WHO Health Technology and Pharmaceuticals cluster [34].
- B. **UMC, Sweden:** an independent, not-for-profit foundation, a center for international scientific research, based in Sweden – closely associated with WHO, since 1978. The principal function of the UMC is to manage the international database of ADR reports received from National Centers [35].
- C. **The National Pharmacovigilance Centers:** National Centers have played a significant role in increasing public awareness of drug safety. This development is partly attributable to the fact that many national and regional centers are housed within hospitals, medical schools or poison and drug information centers, rather than within the confines of a drug regulatory authority [36].
- D. **Hospitals:** A number of medical institutions have developed adverse reaction and medication error close watch systems in their clinics, wards and emergency rooms.
- E. **Academia:** Academic centers of pharmacology and pharmacy have played an important role through teaching, training, research, policy development, clinical research, ethics committees (institutional review boards) and the clinical services they provide [37].
- F. **Health Professionals:** Originally physicians were the only professionals invited to report as judging whether disease or medicine causes a certain symptom by exercising the skill of differential diagnosis [38].
- G. **Patients:** Only a patient knows the actual benefit and harm of a medicine taken. Direct patient participation in the reporting of drug related problems will increase the

efficiency of the pharmacovigilance system and compensate for some of the shortcomings of systems based on reports from health professionals only.

Necessity of Collaboration

Pharmacovigilance system implementation is the need which is possible by collaboration between academia, health care providers including pharmacist, patient, manufacturer, government, media, and civil society, UMC Sweden operating under (WHO), FDA, Isop and other international organization working on drug safety [39]. There are five WHO Collaborating Centers working for pharmacovigilance, each in specialist areas. In addition to UMC in Sweden, these are in India, Morocco, the Netherlands, and Norway.

- A. **The center in Rabat (Morocco):** Became a WHO Collaborating Centre in 2011. The Rabat center assists WHO by building capacity in the WHO Eastern Mediterranean Region, in francophone, and Arabic countries.
- B. **Pharmacovigilance Centre Lareb (Netherlands):** Netherlands' national pharmacovigilance center for Pharmacovigilance in Education and Patient Reporting. It became a WHO Collaborating Centre in 2013.
- C. The Centre in Norway was established in 1982 in Oslo at the Department of Pharmacoepidemiology at the Norwegian Institute of Public Health, funded by the Norwegian Government.
- D. Founded in 2010, the Pharmacovigilance Program of India (PvPI) was designated as a specialist center by WHO in Geneva, 2017 [40], [41].

Role of Pharmacist in the Management of ADRs

- In the United States alone, DDIs contribute to 20% of all adverse drug events, which cause nearly 770,000 deaths and result in \$30 billion to \$180 billion in healthcare expenditures and four hospitalizations per

1,000 people annually. A pharmacist plays a pivotal role in the identification, detection, prevention, and management of drug-drug interactions, drug-food interactions and ADRs [42, 43]. Pharmacist can carry out such activities in inpatient setting, while taking part in viewing charts during ward rounds, and during medication management while dealing with prescriptions.

- The prevalence of patients who visited multiple hospitals with the same or similar condition was nearly 40% among patients attending government outpatient departments in Hong Kong, 23% among primary care patients in Japan, and 23.5% among outpatients in Taiwan [44]. Patients who receive medical care from multiple health care providers, particularly from different hospitals, are more likely to suffer adverse drug reactions (ADRs). Some researchers suggested that pharmacists use computerized screening software to identify potential drug therapy problems and prevent adverse events. Others suggested use of CPOE with CDS to improve medication errors.
- The intervention of pharmacists by organizing lectures and group discussions thus providing information about the importance, seriousness, preventability and necessity of reporting shows heightened improvement of knowledge, attitude and perception about ADRs.
- All health professionals play their respective roles in balancing between benefits and risks of medication when it is introduced in the market. However, the expertise of a pharmacist about a drug, especially if newly marketed, play a more important role in ADRs reporting to the authorities which helps in either withdrawing the product from the market or cause labelling changes [45]. Following Thalidomide-Induced Phocomelia tragedy, Bowles urged ADR reporting as a factor in accreditation of pharmacists back in 1964 [46].

- Pharmacists working in community pharmacy have an added advantage of detecting and reporting ADRs while dealing with on the counter prescriptions and herbal products. In a community pharmacy, a pharmacist may not have direct and definite patient list but the patients coming to the same pharmacy to refill their prescription gives the pharmacist an opportunity to detect a possible ADR that the patient might be experiencing and can help in the management and the reporting of the said ADR. Pharmacist consultation skills need to be reviewed if MURs are to realize their intended aims [47].

Role of pharmacist in Pharmacovigilance

The contribution of the pharmacist to pharmacovigilance should, however, not be limited to ADR reporting. Especially, hospital pharmacists can play a significant role in ADR reporting because the most serious adverse drug events occur in hospitals, and ADRs account for a substantial proportion of hospital admissions [48]. The pharmacist could be a coordinator between different members of healthcare team and the patients, to ensure both vigilance and compliance. Thus, involvement of pharmacists in health management system is becoming very crucial day by day. Pharmacists are involved in providing health care facilities as well as suggesting medical staff on proper selection of drugs. They also plan, monitor and evaluate drug programs to improve health and reduce health inequalities [49], [50]. Hospital pharmacists ensure that medicines are managed safely and effectively so that they are appropriate for the age, sex, body weight and clinical status of the patient. Community pharmacists on the other hand come in direct contact with the public and they not only dispense medications but also counsel patients regarding general health topics such as diet, exercise, stress management, over-the-counter medications etc. [51], [52]. Some community pharmacists also provide specialized services to help patients with diabetes, asthma,

smoking cessation, drug addiction, and patients with high blood pressure. The role of pharmacists in pharmacovigilance systems is amplified under Affordable Care Act or the current health care reform, because people who otherwise had no insurance, now qualify for insurance; and this could increase the demand for pharmacy services. More pharmacists will be required in delivering health education, including education on drug-drug interaction [53]. Pharmacists can prevent drug interaction, counsel patient regarding the disease and medication e.g. providing information, advice and assistance about medication and therapy due to their access of interpersonal communication. The changing role of the pharmacist from traditional 'drug dispenser' concept towards 'pharmaceutical care provider' expanded the role of pharmacists. Thus, pharmacists can play a key role in preventing drug abuse by providing clear information about the adverse effects of medications [54]. Furthermore, the development of electronic information systems has been a milestone in identifying and intervening drug related problems such as dosage, adverse reactions, interactions, compliance or ineffectiveness.

Conclusion

Being drug expert and mentor of safe and effective drug use, pharmacists have important role play in detection, report, monitoring along with prevention of ADRs. The lack of apprehension still exists among pharmacists who are confined to transition from product oriented to patient oriented. The gap can be minimized through continued professional development programs as well as reinforcing knowledge base in undergraduate level. An empowerment and engagement of community pharmacists to patient record check and electronic reporting may also reduce ADR related events. Without adequately identifying and fulfilling training needs of pharmacists and other health care professionals, the efficiency of national pharmacovigilance systems is unlikely to improve, which may compromise patient

safety. To reach this goal, regulatory bodies should make legislations to encourage pharmacists to be actively involved in the system. Besides their active participation, their assigned role should have a broader spectrum to obtain the maximum benefit based on their expertise. Effective use of pharmacists' workforce will improve the outcome of the pharmacotherapy as well as decrease global health costs.

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