



■ Review Article

Pharmacovigilance and Its Importance for Primary Health Care Professionals

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Pharmacovigilance is used to detect, assess, understand, and prevent the adverse effects of medications. The need for safety monitoring has evolved around unfortunate incidents in history, with deaths caused by anesthesia and congenital malformations from thalidomide use. Reports from adverse drug reactions (ADRs) are stored in a global database and can be used to evaluate the associations between various medications and associated ADRs. Clinicians play an important role in the recognition and reporting of ADRs to national pharmacovigilance centers (NPCs). The purpose of NPCs is to make the clinicians understand their functions, including the monitoring, investigation, and assessment of ADR reports, along with periodical benefit-risk assessments of medications via multiple sources. A case study on NPCs and the types of safety issues evaluated by them are provided to illustrate their role in medicine safety surveillance. ADR monitoring was also combined with vaccine safety surveillance approaches. Overall, this study will provide insights to clinicians on the importance of pharmacovigilance in maintaining patient safety with the proper use of medications.

Keywords: Drugs; Drug-Related Side Effects and Adverse Reactions; Patient Safety; Pharmacovigilance

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INTRODUCTION

Pharmacovigilance is defined as the science of detection, assessment, understanding, and prevention of adverse effects of drugs or other related problems.¹⁾ The importance of pharmacovigilance was first highlighted in 1848, when a girl named Hannah Greener from England passed away after being administered chloroform for anesthesia to remove an infected toenail. Due to concerns around the safety of using anesthetics, the Lancet set up a commission to tackle this issue, encouraging doctors to report deaths caused by anesthesia.²⁾

In 1961, McBride³⁾ from Australia wrote to the Lancet, reporting his suspicion of thalidomide ingestion during pregnancy causing an increase in congenital malformations in babies. Thalidomide was marketed in 1957 to alleviate morning sickness and was deemed to be safe for use during pregnancy by the manufacturer.³⁾ However, thalidomide use during pregnancy resulted in abnormal fetal development and limb deformities (phocomelia) in 46 countries worldwide. This highlighted the importance of safety monitoring of drugs post-marketing, independent of any industrial influence. The thalidomide tragedy served as a catalyst for the formation of the World Health Organization (WHO) International Drug Monitoring Program and the strengthening of regulatory frameworks on drug safety. From this incident, the spontaneous reporting of adverse drug reactions (ADRs) became systematic, organized, and regulated.

The WHO-Uppsala Monitoring Centre (WHO-UMC), based in Sweden, was established in 1978. It manages Vigibase, a WHO global database of individual case safety reports. It has over 18 million reports of suspected adverse effects of medicines submitted since 1968 by member countries of the WHO Program for International Drug Monitoring.^{4,5)} This database can be used to evaluate the association between various medications and related ADRs. Medication safety monitoring was especially important during the coronavirus disease 2019 (COVID-19) pandemic to determine the safety of drugs, including new

drugs, such as remdesivir, or repurposed drugs, such as lopinavir/ritonavir, against COVID-19.⁶⁾

ROLE OF CLINICIANS IN PHARMACOVIGILANCE AND DRUG SAFETY

Clinicians play a crucial role in preventing ADRs by recognizing, managing, and reporting ADRs to the national pharmacovigilance centers (NPCs). Safe and rational prescription of drugs require therapeutic reasoning and appropriate selection of drugs for each patient.⁷⁾ Factors that may increase the risk of ADRs include age, medication error, polypharmacy, and patient-specific risk factors, such as comorbidities.^{8,9)}

Recognizing ADRs and differentiating them from other diseases or comorbidities is challenging and requires the clinicians to have knowledge of the clinical pharmacological principles of ADRs, including their types, dose-relatedness, hypersensitivity reactions, time relationships, and risk factors. For example, long-term complications, such as atypical femoral fractures secondary to bisphosphonates, may only occur after prolonged exposure.¹⁰⁾ Discontinuing medications may also cause rebound of medical conditions, such as the increased risk of osteoporosis with denosumab cessation.¹¹⁾ Table 1 summarizes the different classifications of ADRs.¹²⁾

In addition to managing complications, clinicians also need to communicate and counsel patients to ensure ongoing compliance, treatment of underlying conditions, and to maintain appropriate documentation of the patient's clinical records to avoid further exposure to the medication. Finally, clinicians should be encouraged to report ADRs to ensure that the safety profile of medications is logged in and recorded nationally, which assists in formulating regulatory actions to minimize the risk to consumers.

Table 1. Classification of adverse drug reactions

Type of reaction	Description
A: Dose related	Exaggerated expected effects from medicines at usual doses e.g.) bleeding with warfarin, bradycardia with beta-blockers
B: Idiosyncratic	Unrelated to pharmacological properties e.g.) Steven's Johnsons syndrome with allopurinol
C: Dose & time related	Related to cumulative drug use over time e.g.) adrenal insufficiency with corticosteroids
D: Delayed	Apparent only use of medicines after time e.g.) skin cancers with topical tacrolimus
E: Withdrawal	Associated with withdrawal or medication cessation e.g.) rebound tachycardia with stopping beta-blockers
F: Failure of therapy	Associated with unexpected failure of therapy, possibly due to drug interaction e.g.) St. John's Wort reducing efficacy of combined oral contraceptives
G: Genetic	Associated with irreversible genetic damage e.g.) phocomelia after thalidomide
H: Hypersensitivity	Associated with an immune-mediated response to medicines in a sensitized patient e.g.) amoxicillin and interstitial nephritis (immune complex)

Adapted from Centre for Pharmacy Postgraduate Education. Adverse drug reactions, part 1 - adverse drug reactions and medicines safety [Internet]. Manchester: Centre for Pharmacy Postgraduate Education; 2021 [cited 2021 May 1]. Available from: <https://www.cppe.ac.uk/programmes/ldr1-e-01>.¹²⁾

ROLES OF NATIONAL PHARMACOVIGILANCE CENTERS

The main role of NPCs is to coordinate national ADR monitoring programs. This usually involves monitoring, investigating, and assessing ADR reports received from healthcare professionals and product license holders.¹³⁾

As product license holders are responsible for their products in the market, they are obliged to report all relevant safety information related to their products and comply with post-marketing requirements. This includes a prompt response to requests for information required to conduct a benefit-risk evaluation so that appropriate regulatory actions can be taken. The International Conference on Harmonization (ICH) and Council for International Organisations of Medical Sciences (CIOMS) provide scientific guidance for pharmacovigilance and risk management of medications throughout their life cycle, from preclinical and clinical development to post-marketing stages.¹⁴⁾ Pharmaceutical companies may fill the CIOMS form to report suspected ADRs following a standardized approach for reporting that has been shown to be useful and effective.¹⁵⁾

As NPCs have to investigate ADRs, spontaneous ADR reporting should be done immediately after identification by clinicians, preferably within three days (or within 24 hours for severe ADRs, such as death). Investigations of ADRs enable causality assessment, which should follow a standardized approach. The two commonly used methods for causality assessment include applying the WHO-UMC criteria and the Naranjo algorithm. The former utilizes an expert panel and is simpler and more time-efficient, while the latter uses a logistic approach with objective scores and probabilities, which are less prone to subjective variations.^{16,17)} The findings of these ADR reports, investigations, and causality assessments are submitted to the global adverse event database at WHO-UMC.⁴⁾

NPCs receive notifications regarding possible safety and risk issues from foreign regulatory agencies, product license holders for medications, and the WHO. A Periodic Benefit-Risk Evaluation Report (PBRER) contains comprehensive, concise, and critical analysis of new or emerging information on the risks of a medicinal product and its benefits in approved indications.¹⁸⁾ The format and content of this document is based on ICH technical requirements and guidelines for periodic safety update reporting. This ensures a structured and systematic approach to define a medicine's benefit-risk profile, including its strengths, limitations, or uncertainties of available evidence.¹⁹⁾ However, a committee of relevant stakeholders may be required to review the data to ensure a multisectoral approach to review the PBRER for decision-making and use it as a tool to improve the quality of communication with other stakeholders and consumers.²⁰⁾

Based on the information received, the center will conduct risk minimization activities, which may include safety alerts, restrictions, and controlled access to prescribers, or in rare instances, de-registration of the product from the market. Communicating safety information to relevant stakeholders, especially prescribing clinicians, may occur in

the form of a "Dear Healthcare Professional" letter specifying any updates on the use of a particular medicine. Content and communication plans, such as intended recipients and mechanism of dissemination, require mutual agreement between the license holders and NPCs.²¹⁾ These regulatory risk communications have resulted in significant changes in targeted prescribing with an impact on clinical outcomes.²²⁾

Some NPCs also manage product defect reports, and may include cosmetics and personal care products in their portfolios. For example, the US Food and Drug Administration set up the Center for Food Safety and Applied Nutrition's Adverse Event Reporting System in 2016, a public repository of adverse events related to foods, dietary supplements, and cosmetics.²³⁾

Finally, some NPCs collaborate with academic and healthcare institutions to conduct research on drug safety. This may involve ongoing monitoring or active surveillance of specific medications or target groups for safety issues.²⁴⁾ They also evaluate the impact of regulatory interventions on patient safety.²⁵⁾

CASE STUDY

In Brunei Darussalam, the National Adverse Drug Reaction Monitoring Center formed in 1998 is the NPC. It joined the WHO International Drug Monitoring Program in 2005. Given the need for technical expertise in the evaluation of reports and PBRER, a Pharmacovigilance Advisory Committee was established in 2018. The committee members have the following specialties: geriatrics, pediatrics, internal medicine, public health, primary care, and pharmacy. This committee makes recommendations to the Medicines Control Authority on matters related to the safety of medicines via information on ADR reports, causality assessments, emerging safety issues identified in other countries, and PBRER evaluations. Table 2 illustrates examples of potential safety issues received from overseas reports and regulatory authorities between July, 2019 and June, 2020.^{26,27)}

Between July 2019 and June 2020, the NPC received an ADR report of a patient who sustained intracranial bleeding while on dabigatran, which demonstrated the importance of causality assessment. Non-vitamin K antagonist oral anticoagulants for patients with atrial fibrillation (to reduce the risk of embolic stroke) cause less intracranial bleeding compared to warfarin.²⁸⁾ A review of the patient's clinical records revealed that the patient had a history of cerebral amyloid angiopathy. This meant that the patient was not clinically eligible to start antiplatelet or anticoagulant therapy, so this complication was not caused by the medication alone.

There is a need to improve the technical skills of personnel for vaccine safety surveillance. Thus, in collaboration with WHO as part of the implementation of the Global Vaccine Action Plan, a training workshop on Vaccine Pharmacovigilance and Immunisation Safety Surveillance was held in the Ministry of Health, Brunei Darussalam in 2019. This was timely given the need to monitor ADRs following the off-label use of medications for the treatment of COVID-19 and the global implementation of COVID-19 vaccines to curb the pandemic.²⁷⁾

Table 2. Examples of potential safety issues received between July 2019–June 2020

Medication	Safety alert
Fluoroquinolones	Concomitant use with ACEI or ARBs contraindicated in patients with moderate to severe renal impairment (CrCl 30 mL/min) and in older patients ²⁶⁾
Montelukast	Monitor for neuropsychiatric reactions, e.g., nightmares, depression, anxiety, change in behavior, speech impairment (stuttering), and obsessive-compulsive symptoms for all age groups
Hydroxychloroquine	Risk of serious and life-threatening QT prolongation, torsades de pointes, syncope, cardiac arrest, and sudden death, particularly in combination with other medications known to prolong QT interval ²⁷⁾
Denosumab	Risk of multiple vertebral fractures after stopping, to consider benefits and risks before initiating treatment with denosumab, to cover with an alternative bone sparing agents when stopping denosumab ¹¹⁾
Parenteral nutrition containing amino acids and/or lipids	Risk of toxic degradations of ingredients when exposed to light, which may lead to adverse outcomes in pediatric patients less than 2 years old; particularly oxidative stress related adverse outcomes, e.g., respiratory distress syndrome, bronchopulmonary dysplasia, periventricular leukomalacia
Methotrexate	Risk of fatal overdose due to inadvertent daily instead of weekly dosing
Fentanyl	Risk of overdose when used in opioid-naive patients
Empagliflozin	Risk of peri- and postoperative diabetic ketoacidosis in surgical patients with SGLT2 inhibitors, recommend temporary discontinuation before scheduled surgery
Domperidone	No longer licensed or indicated for use in children younger than 12 years old or those weighing less than 35 kg due to lack of efficacy
Ticagrelor	Safety signal of severe cutaneous adverse reactions

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CrCl, creatinine clearance; SGLT2, sodium-glucose co-transporter 2.

VACCINE SAFETY SURVEILLANCE COMPARED TO ADVERSE DRUG REACTION MONITORING

Use of vaccines is an important and cost-effective public measure for reducing childhood morbidity, mortality, and risk of vaccine-preventable infectious diseases. Similar to medications, vaccines must be stringently evaluated for their safety, efficacy, and quality. However, as vaccines are administered to healthy people to prevent diseases, there is a need to lower the risk and increase the standard of safety. Thus, investigations of adverse events following immunization (AEFI) and causality assessments follow a more stringent process, requiring training and technical expertise. There may also be issues with vaccine hesitancy owing to misinformation or emerging safety concerns, which need to be managed proactively by NPCs.²⁹⁾

Recently, the COVID-19 pandemic has necessitated the implementation of large-scale immunization programs utilizing newly developed vaccines. Although these vaccines have been shown to be safe and efficacious in phase 3 trials,^{30,31)} there is a need for post-marketing surveillance, which should be actively undertaken by NPCs.³²⁾ However, specific details of AEFI investigations, causality assessments, and active vaccine safety surveillance are outside the scope of this paper.

APPLYING PHARMACOVIGILANCE IN CLINICAL PRACTICE

Effective pharmacovigilance relies on consistent, high-quality data from clinicians regarding ADRs, especially rare adverse effects that may require international databases to detect safety signals.³³⁾ However, there is significant international variability in pharmacovigilance approaches. For example, there is a greater reliance on industry funding to oversee post-marketing surveillance in Europe, while in North America, this tends to be via publicly funded programs.³⁴⁾ In Asia,

pharmacovigilance is less developed, with significant variability depending on the geographical, cultural, and medical practices of each region.³⁵⁾

Most doctors understand the importance and relevance of pharmacovigilance in clinical practice. However, there is low awareness of pharmacovigilance programs and practical aspects, such as where and what to report in terms of ADRs.^{36,37)} Thus, educational and training programs to improve awareness and quality of ADR reporting are required. This can be achieved through lectures, small interactive learning groups, and practical demonstrations in real-life clinical situations.³⁸⁾

Much work remains to be done for curriculum development and standardization of the competencies required for pharmacovigilance. Generally, functional and behavioral competencies should be based on different levels: clinicians collecting information or evidence regarding ADRs, processing and distilling information, and decision makers regarding any changes in outcomes based on ADRs.³⁹⁾ A set of proposed core competencies to support pharmacovigilance include analytical and assessment skills, communication skills, and leadership and system thinking skills for identifying and preventing ADRs.⁴⁰⁾

It is challenging to demonstrate a clinician's pharmacovigilance performance in terms of its impact on patient safety. Thus, surrogate markers, such as the number and quality of ADRs reported, are currently used.⁴¹⁾ Participation of healthcare professionals in pharmacovigilance will lead to beneficial changes in practices related to prescribing, shared therapeutic decision-making, and communication with patients. However, further research is required to identify and measure the abstract benefits of additional patient engagement by primary care physicians from a prescriber or regulator's perspective.⁴²⁾

CONCLUSION

Pharmacovigilance is important for medication safety monitoring and post-marketing safety surveillance, as ADRs may occur after the completion of randomized controlled trials. Clinicians play an important role in recognizing and reporting ADRs so that NRCs can record and evaluate these concerns and take the required action to maintain patient safety associated with the use of medicines.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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