

Pharmacovigilance and the reporting of adverse drug reactions

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Abstract

Adverse drug reactions continue to be a major public health problem, negatively affecting patient care, having the potential to cause harm, and burdening limited healthcare resources. Clinical trials are able to detect only the most common side effects of a drug before licensure, highlighting the importance of post-marketing surveillance and pharmacovigilance to detect rare adverse drug reactions. The safe use of medicines is a priority for all healthcare professionals, regulatory authorities, pharmaceutical industries and the public, however, under-reporting of adverse drug reactions is a global problem. Educational interventions for health care professionals can improve knowledge, attitudes and the practice of adverse drug reaction reporting. Evidence has shown some benefits of pharmacists' involvement in adverse drug reaction reporting, hence they can play an important future role in pharmacovigilance.



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Introduction

The World Health Organization (WHO) defines pharmacovigilance as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems".¹ However, the

term is unfamiliar to most people and there is a lack of understanding regarding the principles and processes of pharmacovigilance as well as the benefits of reporting adverse drug reactions (ADRs).²

An ADR is defined as "any response to a drug which is noxious and unintended, and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function".¹ ADRs have the potential to cause significant harm to patients.^{3,4} They can also increase morbidity and mortality, adding to the suffering of patients.^{5,8} Although medicines are prescribed with the intention to treat and ameliorate illnesses, no medicine is without risk. It is therefore essential that all healthcare professionals (HCPs) have sufficient knowledge of ADRs in order to better manage patient outcomes.¹

Importance of pharmacovigilance and ADR reporting

Pharmacovigilance is a broad concept, and includes the re-evaluation of marketed drugs, risk management, communicating drug information and promoting the rational use of drugs.¹ Pre-marketing clinical trials do not have the statistical power to detect rare ADRs, nor do they have sufficiently long follow-up to identify delayed ADRs or effects from long-term exposure.¹ In view of this, pharmacovigilance

plays a prominent role in establishing the safety profile of marketed drugs.^{1,2}

Part of the process of evaluating drug safety needs to happen in the post-marketing phase. The stronger the pharmacovigilance system and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early approval of new drugs with the promise of therapeutic advances.¹ Careful safety monitoring is, however, not confined to new drugs or to the significant therapeutic advances of new drugs.¹ It also has an important role to play in the introduction of generic medicines and in the review of the safety profile of medicines already available, where new safety issues may have been identified.² Pharmacovigilance is also a clinical discipline, which contributes towards safety and serves as an indicator of the standards of clinical care practised. Healthcare practitioners can therefore use patients' positive and negative experiences of their treatment to contribute to medical science and to improve the understanding of disease and of the medicines.¹

Globally, ADRs are responsible for many deaths.^{7,8-11} In the United States, ADRs contribute to more than 100 000 deaths annually and are among the top 10 leading causes of death.⁷ The United Kingdom showed a 16% incidence of hospital-acquired ADRs amongst hospital inpatients, while Germany showed an even higher 38% incidence.⁸ ADRs are also a major cause of, and responsible for, a substantial number of hospital admissions each year.¹²⁻¹⁹ In South Africa, an observational study estimated that 6.3% of hospitalised patients were admitted as a direct result of an ADR, while a further 6.3% of patients developed a significant ADR while in hospital.²⁰ Another cross-sectional survey estimated that ADRs contributed to the death of 2.9% of medical admissions, with 16% (56; n=357) of deaths in the wards being ADR-related.⁶

Pharmacovigilance has constantly grown in importance over the last 15 years, relating to the number of ADRs reported and to the fact that several hospital admissions are due to ADRs.²¹

Reporting structures for ADRs in South Africa

In South Africa, pharmacovigilance initiatives are largely determined by three key participants, namely the regulators and the pharmaceutical industry, public health programmes and HCPs.²² The South African Health Products Regulatory Agency (SAHPRA), previously the Medicines Control Council (MCC), applies standards stipulated by the Medicines and Related Substances Act (Act 101 of 1965) which governs the manufacture, distribution, sale, and marketing of medicines. The regulations to the Medicines and Related Substances Act (Act No. 101 of 1965), clearly stipulate that any new or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to ADRs, and the risk management activities associated with these concerns, must be reported to SAHPRA within a stipulated time frame.²³

In 1987, the National Adverse Drug Event Monitoring Centre (NADEMC), a unit of the then MCC, was established to facilitate ADR monitoring. The NADEMC manages the collection and review of voluntarily submitted ADR reports from health professionals, to detect signals of unknown or poorly understood ADRs. South Africa also became the first African member of the WHO International Drug Monitoring Programme in 1992.²²

Synergies between pharmacovigilance and the related activities of disease surveillance and health system strengthening have resulted in the recognition of pharmacovigilance as a critical public health discipline in South Africa, requiring integration into all aspects of health care.²² Pharmacovigilance activities have evolved from passive regulatory reporting to encompass active surveillance systems. The HIV/AIDS and tuberculosis (TB) epidemics stimulated pharmacoepidemiological research into the risks associated with medicines used in the standardised regimens of mass treatment programmes. Specific safety concerns, supported by local data from cohort studies, have prompted major changes to national and international treatment policies.²²

With the introduction of National Health Insurance (NHI) in South Africa, the government has committed itself to provide all South Africans with quality affordable health services based on their health needs regardless of their socioeconomic status.²¹ One of the initiatives of the National Department of Health (NDoH), in response to the urgent need to increase quality of care across the whole health system, was the development of the National Core Standards (NCS) for all health establishments in 2011.²¹ The National Health Act (Act 61 of 2003) was subsequently amended on 24 July 2013²⁴ and an independent public entity, the Office of Health Standards Compliance (OHSC), was established. The role of this new regulator is to protect and promote health and safety in health services by monitoring and enforcing compliance with certain quality norms and standards within all health establishments.²³

The NCS are structured into seven crosscutting domains, where quality or safety might be at risk for a health establishment.²¹ The domain of 'Clinical Support Services', which was also identified as one of the six fast-track priority areas for health establishments in South Africa, covers specific services essential in the provision of clinical

care, including the availability of medicines and systems to monitor the effectiveness of the care provided to patients.²¹ According to the standards, adverse events or patient safety incidents must be identified and managed promptly, to minimize patient harm and suffering.²¹ Health establishments are required to have a clear system in place to actively report adverse events, adverse reactions to drugs or severe side effects, and in response manage identified ADRs, which includes patient care.²¹ Each health institution must therefore have an effective pharmacovigilance system in place to monitor and manage ADRs, to be able to comply with the NCS.^{21,23} Evidence of compliance is measured through an audit tool, stipulating the following standards in terms of ADRs:²⁴

- A clear system for the management of ADRs must be in place in a health institute.
- Standard operating procedures (SOPs) are required for the monitoring of ADRs.
- The minutes of the committee, which deals with ADRs, are required and should demonstrate that actions have been taken to report/analyse and take appropriate action regarding ADRs.

In 2011, the NDoH Pharmacovigilance Centre for Public Health Programmes established a decentralised system for pharmacovigilance, with targeted spontaneous reporting for antiretroviral (ARV) and TB medicines, aimed at using ADR reports as a clinical tool to improve ARV and TB medicine use.²⁵ The rollout of the decentralised pharmacovigilance programme included training throughout the provinces.²⁶ A one-day pre-training site visit to ascertain training needs and readiness for the programme was followed by a one-day interactive pharmacovigilance training session for healthcare providers.²⁶ As part of this initiative, a pharmacovigilance bulletin was published which provided feedback on the activities of the programme and the pharmacovigilance systems in place throughout the country.²⁶

At provincial level, initiatives were taken to strengthen pharmacovigilance. One example is the Gauteng Provincial Pharmacy and Therapeutics Committee (GPPTC), which commenced with a revitalisation PTC programme in 2012 and subsequently established a subsidiary Safety and Quality committee. The duties of the committee included the development and maintenance of medicines safety systems, with specific objectives to manage activities relating to procurement, distribution and the use of medicines, and to establish and maintain a system for reporting medicine safety i.e. ADR reporting, medication errors and quality problems.²⁷ The GPPTC published its first Pharmacovigilance Bulletin in April 2017. The bulletin gives feedback about the ADRs reported in the province and highlights some challenges and lessons learned on educating HCPs and promoting communication on pharmacovigilance activities.²⁷

When the MCC was restructured to SAHPRA in 2017, new regulations were adopted, which provide the opportunity to prioritise pharmacovigilance as a well-resourced, successful regulatory function of the new organisation. Furthermore, there is international recognition of the need to strengthen and prioritise post-marketing pharmacovigilance activities. This approach could improve monitoring and evaluation of already-marketed products, and adapt decisions for local conditions.²²

Reasons for non-reporting of ADRs

Under-reporting of ADRs is a worldwide phenomenon and the predictors of under-reporting have been described by many authors, although these reasons differ between studies and settings.²⁸ Drug safety surveillance strongly relies on spontaneous reporting of adverse drug reactions (ADRs) and thus depends on the personal motivation of HCPs to report observed ADRs.² However, spontaneous reporting in hospitals is scarce and several obstacles have been identified for this.²⁹

Low reporting rates of ADRs are incorrectly referred to by the term 'under-reporting', which is one of the major limiting factors of spontaneous reporting systems and a challenge in pharmacovigilance.¹ Several factors contribute to under-reporting of ADRs, such as a lack of knowledge about pharmacovigilance or the particular reporting system, uncertainty regarding the causal relation between the ADR and the drug, lack of time, and the belief that only serious or previously unknown ADRs should be reported.³⁰ More determinants of under-reporting, include lack of knowledge of the forms for reporting, ignorance of the rules and procedure for reporting, and not being sure of the type of reactions to be reported.²⁵

Many factors are associated with the under-reporting of ADRs among HCPs. These factors have been broadly classified as personal and professional characteristics of health carers, and their knowledge and attitudes to reporting. What is commonly referred to as the 'seven deadly sins' for non-reporting of ADRs include the following:³¹

- i. Attitudes relating to professional activities;
- ii. Financial incentives: rewards for reporting;
- iii. Legal aspects: fear of litigation or enquiry into prescribing costs;
- iv. Ambition to compile or publish a personal case series;
- v. Problems associated with ADR-related knowledge and attitudes (complacency: the belief that very serious ADRs are well documented by the time a drug is marketed; diffidence: the belief that reporting an ADR would only be done if there was certainty that it was related to the use of a particular drug; indifference: the belief that the single case an individual doctor might observe could not contribute to medical knowledge);
- vi. Ignorance: the belief that it is only necessary to report serious or unexpected ADRs; and
- vii. Excuses made by professionals (lethargy: the procrastination and disinterestedness in reporting or lack of time to find a report form and other excuses).

Potential barriers for the spontaneous reporting of ADRs according to the HCPs in a South African hospital-based study were that they do not know how to report, where to report and when to report ADRs.²⁸ Other reasons given included 'Concern that the report may be wrong', 'nothing would be done with the data' and the 'medical practitioners' lack of time to look actively for ADRs while in the ward.²⁸

Interventions to improve reporting of ADRs in hospitals

The reporting of ADRs in hospitals is very important because innovative new drugs are often used for in-patients, therefore severe

ADRs are most likely to be seen in hospitals, ADRs can be detected at an early stage and spontaneous reports can be more accurate.³² Improved hospital-based reports could make important contributions to future care.²⁹ However, there is a poor record of ADR reporting in hospitals. Thus, the opinions and attitudes of hospital physicians about the problems experienced with spontaneous reporting of ADRs and the ways to solve these problems are very important.³²

Previous research has demonstrated that educational activities play an important role in improving the ability of HCPs to detect and report ADRs.³³ Spontaneous reporting of ADRs can be successful only if HCPs at the first level of contact with patients have significant insight into the importance of pharmacovigilance, together with the skills necessary to identify and report ADRs.³³

Several studies investigated reasons for lack of ADR reporting and what can be done to improve reporting. Evidence has shown that the factors dissuading medical practitioners from spontaneous reporting are mostly related to the lack of understanding of the reporting procedure (95.2%), lack of adequate clinical knowledge (81.8%) and lack of time to actively look for and report the ADRs.³⁴ Medical practitioners also have many misperceptions about the entire procedure and are apprehensive that it can increase their workload or they might be wrong in identification of ADRs.³⁴ To improve spontaneous reporting rates, HCPs suggested training programmes, an uncomplicated reporting system with quick feedback regarding their specific report and also all other reports received by the pharmacovigilance system. Gestures like acknowledgment of the receipt of the report and an appreciation note would also help, motivating them to continue the pharmacovigilance activities.³⁵

Evidence has shown that interventions such as continuous education of HCPs about pharmacovigilance and ADRs, increased availability of report forms in hospital wards, pharmacists being available in hospital wards, and HCP education and training, resulted in better awareness, attitudes and knowledge towards ADRs.^{31-33,37-39} A pharmacist-driven pharmacovigilance system implemented in a South African hospital, which included training to improve ADR reporting, contributed significantly to HCPs gaining knowledge about the ADR reporting system, among medical practitioners, pharmacists' assistants and nurses.²⁹ Similarly, a study conducted in Istanbul amongst community pharmacists showed that educational interventions improved the knowledge, attitudes and practises of ADR reporting.³⁶

A number of other tools can be used to increase awareness of pharmacovigilance and remind HCPs to report ADRs. A study conducted in South Africa showed that posters displayed in hospital wards, explaining ADRs and the reporting thereof, prompted HCPs to report ADRs.²⁹

In order to address some of the determinants of under-reporting found in a study conducted in a tertiary centre in Northern Nigeria, it was proposed that ADR reporting guidelines should be made available in the form of booklets and posters at conspicuous locations in healthcare facilities. These will then serve as a constant reminder to HCPs.⁴⁰

Role of the pharmacist in pharmacovigilance

The pharmacy profession has undergone many changes over the years. The role of the pharmacist is now not only concerned with medicines and their preparation, but has moved to a more patient-oriented approach.³⁰ There has been a significant improvement in the knowledge of pharmacists and appreciation of the role of pharmacists in ADRs.^{28, 36} Pharmacists, both in the community and the hospital sectors, can contribute to the safe use of drugs. In addition to their responsibilities regarding drug dispensing and compliance, pharmacists can have a substantial role in ADR reporting and are an essential resource in safe medication use.⁴¹

In the hospital sector, as seen through various studies and the basic concepts of pharmaceutical care, a pharmacist plays a pivotal role in the identification, detection, prevention, and management of drug-drug interactions, drug-food interactions and ADRs.⁴² Pharmacists can carry out such activities in the inpatient setting, while taking part in viewing charts during ward rounds, and during medication management while dispensing prescriptions. Since pharmacists have extensive knowledge about drugs and therapeutics, their ability to discover and deal with ADRs is very important.⁴²

Conclusions

This review highlights the importance of an effective pharmacovigilance system. It has been shown that the majority of HCPs do not have appropriate knowledge about the ADR monitoring and pharmacovigilance programmes. The active involvement of a well-trained pharmacist for detecting ADRs, implementing pharmacovigilance programmes and training HCPs regarding the need for reporting ADRs, could improve ADR reporting and ultimately patient care. South Africa needs to develop an interconnected system that builds on the significant progress already achieved. This requires strong commitment and leadership by policymakers.

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