

Running Title: Adverse drug reactions and Pharmacovigilance

Adverse Drug Reactions and Pharmacovigilance: a narrative Mini-review of relevant Literature.

Abstract

Background: Adverse drug reactions (ADRs) are known to cause significant morbidity and mortality around the world, and, therefore, need precise terminology and prevention strategies to reduce the global burden on public health and increase safety of patient population. Pharmacovigilance is a powerful tool that detects, assesses and analyses spontaneously reported suspected serious and non-serious ADRs by healthcare professionals and patients, and provides several thoughtful insights for preventing ADRs in healthcare settings. Poor quality reports and underreporting of ADRs limit the efficiency of pharmacovigilance. **Objective:** The main aim of this minireview is to describe precisely definitions of adverse drug reactions, adverse drug events (ADEs) and other related terms, their underreporting, pharmacovigilance, and how to optimize ADRs reporting by professionals and patients to pharmacovigilance. **Methods:** Electronic searches of relevant databases were conducted using keywords for retrieving relevant articles for inclusion in this study. **Results:** Several studies and healthcare organizations have clearly defined ADRs, adverse drug events (ADE) and related terms. Underreporting and poor quality reporting of ADRs remains a global problem. Continuous training of health professionals and patients in ADR reporting to PV is one of the best strategies to optimize the spontaneous reporting of ADRs to pharmacovigilance for early signal detection and prevention of ADRs. **Conclusion:** The standardized use of ADRs terminology tends to focus attention on efforts aimed at eliminating preventable harm from ADEs. ADRs associated with considerable burden on public health and high economic costs need to be prevented by optimal, better quality reporting of ADRs to pharmacovigilance, which is the most powerful tool for preventing ADRs. The key role of healthcare professionals and patients to report ADR spontaneously need no overemphasis and all stakeholders need continuous training in ADRs and pharmacovigilance.

Keywords: Adverse drug reaction, pharmacovigilance, underreporting of ADRs, adverse drug events, signal detection.

Introduction

Adverse drug reactions are unintended and obnoxious reactions of a drug that cause harm to the patient, and these are beyond its therapeutic effect. ADRs are significant cause of morbidity and mortality around the world, and also associated with high healthcare costs and burden on public health. These reactions are often recognized during clinical practice and post-marketing phase and spontaneously reported to pharmacovigilance for identifying causative factors and prevention of their recurrences. [1-3]. Healthcare professionals tend to report the ADRs to several pharmacovigilance centers provided they have good knowledge, attitude and practice towards ADRs and pharmacovigilance or else underreporting of ADRs remains a major healthcare problem worldwide and limit the efficiency of pharmacovigilance[4,5]. The main aim of this mini review is to describe several given definitions of adverse drug reactions and other related terms, their underreporting, and how to optimize their reporting to pharmacovigilance. The significance of this narrative review is that ADRs need to be identified early and reported spontaneously by healthcare professionals to the PV in order to prevent the occurrence and recurrence of ADRs which are globally associated with high morbidity and mortality and great burden on public health. Furthermore, though there are well established databases on ADRs and pharmacovigilance system in high income countries, there is dearth of data on ADRs in low and middle income countries including Saudi Arabia [6-12].

Methods and Results

Search Method

The relevant literature published in English (- 2016) was searched in PubMed, OvidSP and Google Scholar databases. The Boolean operators and keywords used in multiple electronic searches were definitions of adverse drug reactions “AND” adverse drug events, adverse drug reactions in hospitals “AND” pharmacovigilance (PV), OR drug surveillance and monitoring “AND” objectives of pharmacovigilance OR advantages of PV “AND” prevention of ADRs by pharmacovigilance centers. The search strategy and the keywords were modified as appropriate according to the searched database. In addition, the studies listed in relevant articles were hand searched. More than 21,725 articles were retrieved, which were reviewed by two independent reviewers (NAQ & DSAD). Our main focus was

on full articles describing ADRs and PV in healthcare organizations. After removal of duplications [n=8300], no full articles [n=1503], no abstracts [n=821], non-English articles and abstract [n=61], unrelated articles [n=2041] and not accessible papers [n=8901], only 98 papers were left for further review. Finally both reviewers agreed to include 87 published studies in this minireview [Figure 1. Prisma Chart 1].

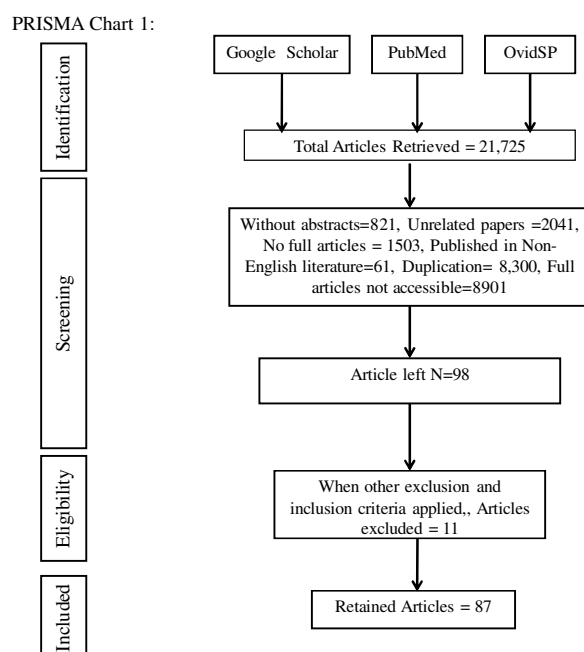


Figure 1 Prisma Chart

Results

Definitions of ADR

The confusion looms large about the definition of adverse drug reactions, adverse drug events, side effects, adverse effects, and other related terms[13]. An adverse drug reaction is defined in different ways in the given literature; “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function” [1] and prevention of disease, disorder or syndrome. There is a causal link between a drug and an ADR as indicated by several indicators such as temporal relation and rechallenge. Side- and excess-effects (lateral effects, parallel effects), also termed as type A(80%) or augmented ADR (predictable or anticipated) based on mechanisms of drug action on targeted or untargeted receptors, are also an undesirable effect of drug, less severe and more frequent

than type B(20%) and comes under adverse drug events (ADEs). Furthermore, a side effect of a drug is an effect, whether therapeutic or adverse, and it is secondary to the one intended. Although side effect is used to describe adverse effects, it can also apply to beneficial, but unintended, consequences of the use of a drug[14,15]. Type A adverse drug reactions are further subcategorized into exaggerated desired effect and undesired effect based on mechanisms of drug action especially involving targeted receptors or otherwise [14,15]. Hurwitz and Wade proposed four categories of ADRs which include side effect, excess effect, allergy or hypersensitivity and idiosyncrasy attributed mainly to digitalis products, bronchodilator drugs, and ampicillin [16]. Later on, DeSwarte and Patterson classified ADRs into eight categories which are overdose, side effect, secondary or indirect effect, interaction, intolerance, idiosyncrasy (primary toxicity), allergy (hypersensitivity) and pseudoallergy (anaphylactoid)[17]. The overdose and interaction are risk factors and the indirect or secondary effect is a physiologic consequence, and for more details are described here[18,19].

Another definition of ADR reflects an injury caused by taking a medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs[20]. Karch and Lasagna defined ADR as any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose[21]. Food and Drug Administration (USA) defined a serious ADE relating to drugs or devices as one in which “the patient outcome is death, life-threatening, i.e., real risk of dying, initial or prolonged hospitalization, significant, persistent, or permanent disability, congenital anomaly, or required intervention to prevent permanent impairment or damage[22]. Edwards and Aronson (2000) defined ADRs as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.” This definition is relatively expanded and more meaningful than WHO description of ADR. ADRs are classified into six types: dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic, continuous), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure)[2]. The latter three ADRs are not mechanisms but their own characteristics of manifestations, and are difficult to diagnose[13]. The capital letters in brackets form mnemonics (ABCDEF) for easy remembrance of ADR types. The management of these

ADRs certainly includes withdrawal of the drug if possible and specific treatment of its effects. The suspected ADRs need to be reported to PV systems, one of the drug surveillance and monitoring methods, to help detect signal and mostly prove causal associations [2]. Furthermore, a variety of variables including timing, the pattern of illness, the results of investigations, smoking and rechallenge could help attribute causality to a suspected ADR [23].

Idiosyncratic adverse drug reactions, also known as type B reactions, pharmacologically unexpected, are rare severe ADRs that unpredictably occur in patients and affect different organs such as the liver, skin, kidney, heart and muscle and are life threatening causing death. Some drugs cause severe generalized hypersensitivity (allergic) reactions (type B). In idiopathic ADRs, the cause is not known. Some suspected unexpected serious adverse reaction (SUSAR) are reported during randomized clinical trials or clinical care in subjects given a drug. These SUSAR are not or may be dose related and not consistent with current information available on ADRs. Severe ADRs are characterized by prolonged hospitalization, being life threatening and requiring intervention to prevent permanent damage and death [1, 14, 15]. Hatwig and colleagues described seven severity levels of ADRs which are level 1 & 2 (mild category), level 3 & 4 (moderate category) and level 5, 6 & 7 (severe category) [24]. Karch and Lasanga classified severity into minor (no intervention), moderate requiring interventions such as change in drug with one day hospitalization, severe in terms of potentially life threatening requiring intensive care and lethal linked with causation of death directly or indirectly [21]. ADRs could be very common ($\geq 1/10$), common (frequent, $\geq 1/100$ and $< 1/10$), uncommon (infrequent, $\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10000$ and $< 1/1000$) and very rare ($< 1/10000$) [25]. A summary of all forms of adverse drug event, ADR and related terms with definitions is shown in Table 1.

Table 1 Definition of adverse drug reactions

Terms	Definition	Types and Remarks
Side effect	A side effect of a drug is an effect, whether therapeutic or adverse, and it is secondary to the one intended.	Type A, more frequent and less severe (pharmacological ADRs)
Excessive effect	Undesirable effect of drug, less severe and more frequent than type B (20%) and comes under ADR and these are lateral or parallel effects	
Allergy (hypersensitivity)	More generalized hypersensitivity (allergic) reactions and due to an immunologic mechanism.	Type B less frequent but very severe (idiosyncratic ADRs)
Idiosyncrasy (primary toxicity)	Idiosyncratic adverse drug reactions are serious ADRs that occur rarely and unpredictably possibly attributed to genetic or acquired enzyme abnormality related toxic metabolites.	
Overdose	Overdose and interaction are risk factors of ADRs	
Side effect	Same as above	
Secondary, indirect effect	The indirect or secondary effect is a physiologic consequence.	
Interaction	Overdose and interaction are risk factors of ADRs	

Intolerance (drug sensitivity)	Drug intolerance, a lower threshold to the normal pharmacologic action of a drug is uncommon, idiopathic, and unpredictable, and may be due to genetic variants of drug metabolism.	
Idiosyncrasy	Same as above and not dose dependent. Receptor abnormality, abnormality of a biological system that is unmasked by the drug, immunological response, drug-drug interactions, or be multi-factorial.	Idiosyncratic ADRs are not related to the known pharmacology of the drug and resolve only when treatment is discontinued
Allergy (hypersensitivity)	Same as above	
Pseudoallergy (anaphylactoid)	An immunologic reaction due to immunoglobulin E and such reactions can occur with NSAIDs.	
Idiopathic ADR	Cause is not known	
ME	A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.	
Harm	Impairment of the physical, emotional, or psychological function or structure of the body and pain or injury resulting therefrom.	
ADE	An injury resulting from medical intervention related to a drug. ADE reflects any harm associated with any dose of a drug, whether the dose is "normally used in man" or not. All ADEs are associated with patient harm, but not all ADEs are caused by a medication error.	Commonly occur during clinical practice and resolve when dose is reduced
Preventable ADE	Harm caused by the use of a drug as a result of an error, i.e., patient given a normal dose of drug but the drug was contraindicated in this patient. These events warrant examination by the provider to determine why it happened.	Increase cost of patients' care, and loss of confidence in physicians.
Non-Preventable ADE	Drug-induced harm occurring with appropriate use of medication, i.e., anaphylaxis from penicillin in a patient and the patient had no previous history of an allergic reaction. While these are currently non-preventable, future studies may reveal ways in which they can be prevented.	Preclude use of drug in most patients as ASRs occur in few patients
ADR	Any response to a drug which is noxious and unintended which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. ADR is a subtype of ADE and all ADRs are ADEs, but not vice versa.	Quality of patients' life is adversely affected. ADRs mimic disease and invites unnecessary investigation
MHRA definition of ADR	An adverse reaction is a response to a medicinal product which is noxious and unintended.	
ADRs during pre-approval (phase) clinical experience	All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.	
Suspected unexpected serious adverse reaction (SUSAR)	These reactions are reported during premarketing phase when randomized clinical trials are in progress.	Even during clinical practice
Acceptability of ADR	Benefit/risk judgment concerning benefit and harm caused by a drug determines the acceptability of ADR. When ADR exceeds harm over benefit is referred as alarming and not accepted. Conversely, when benefit exceeds the harm, ADR is deemed acceptable.	Acceptability of ADR varies in clinical practice in the context of pre-and post-drug administration and the disease
Signal	Denotes possible causal relationship between adverse event and drug, previously unknown or incompletely documented, and more than one report is needed, in case poor quality of the information and seriousness of the event.	Signal is Identified by pharmacovigilance.

Adverse Drug Reactions

Modern medicines are developed in order to relieve people suffering globally, achieve better healthcare outcome, and quality of life but many of them are associated with the occurrence of unintended and obnoxious reactions, which are known as ADRs [2,3]. ADR are known to represent a serious threat to public health around the world since they are not recognized during pre-marketing phase when clinical trials are conducted in humans [1,26]. Adverse drug reactions are also associated globally with significant economic burden

on healthcare system attributable to multiple factors including serious to fatal outcome, increased mortality rate, hospital admissions, bed occupancy, and longer length of stay, productivity loss and absenteeism [1,2,7, 27]. The incidence rate of reported ADRs is low ranging from 0.1% to 5.5% in Saudi Arabia [12,28] which is four times lower than the rate reported from other countries [29,30]. The low incidence of ADRs reporting was attributed to a number of factors including healthcare infrastructure, ADR reporting methods and ADR detection approaches. Drugs mostly involved in the causation of ADRs were anti-infective and anti-epileptic affecting skin with mild rash and urticarial [12]. One study suggested that all ADRs (100%) need to be reported internally to medication safety Unit and Pharmacy and Therapeutics Committee established in hospitals in Saudi Arabia [31]. However, this ideal reporting of ADRs to ADR reporting centers within the healthcare settings or national pharmacovigilance centers is unlikely to be achieved.

Underreporting of ADRs

Adverse drug reactions are underreported by health professionals worldwide. This trend is due to multiple reasons which include but not limited to their knowledge, awareness, practice, and attitude towards ADRs detection and reporting [4,5,32]. The rate of underreporting ranges from 6% to 18.5% [29, 33] that is high and unacceptable, despite PV and other related centers are well established within the healthcare organizations and at national level [4,5,34]. Surprisingly, professionals with positive attitude towards ADRs were found to underreport serious ADEs [35], and some professionals tend to show several attitudinal facets including complacency, and insecurity and fear that result in underreporting of ADRs [36]. Furthermore, professionals mostly suspected ADRs (90%) but underreported (4% to 60%) them to PV centers [37,38] possibly due to time constraints, inability to recognize ADRs, unfamiliarity with the reporting process, causality relationship, unawareness about PV, well-known and mild reactions, immediate management of ADRs, legal liability, complicated ADR reporting form, and unavailability of ADR reporting template in the practice office [4,5 37]. The bottom line is that strategies should be developed for optimal and good quality reporting of ADRs by healthcare professionals around the world. Notably, National Quality Reporting System exists in Ministry of Health, Saudi Arabia that facilitates better reporting of ADRs [39].

Interventions to improve ADR reporting

Notably, most of A type ADRs (up to 80%) are preventable in hospitals provided cost-effective mechanisms are in place [6,40]. Underreporting of ADRs attributed to multiple reasons including lack of experience [4, 5, 41] is a great impediment in the prevention of ADRs in healthcare organizations[1-3]. The high rate of under-reporting can significantly delay signal detection, affects the performance of PV and consequently impact negatively on the public health[42, 43]. Therefore, several strategies including motivational and training programs using the skilled-oriented models directed towards all health professionals were developed for optimizing ADRs reporting [44-46]. Other approaches for improving ADRs reporting were introduction of ADRs in undergraduate curriculum, accreditation of health settings with policies and procedures to report spontaneously ADRs, establishment of PV in healthcare settings, and publication of and free access to ADR bulletin and receiving a feedback (or a customized acknowledgement letter) from the PV [47-49]. These strategies are also directed to improve detection of ADRs by professionals, increase their knowledge, awareness, attitude and spontaneous reporting of ADRs to pharmacovigilance centers[2-5,48]. Although all aforesaid approaches recommended in the improvement of ADRs detection and reporting are important, the post-marketing pharmacovigilance surveillance system is crucial and standalone for monitoring, evaluating, understanding, preventing and improving the reporting of ADRs[1,50]. Health professionals when spontaneously report ADRs contribute significantly to PV success and effectiveness [51] concerning prevention of ADRs, decreased morbidity and mortality and costs, ADR research, pharmacy and clinical practice, and patient safety. The factors that facilitate and impede ADRs reporting to PV are shown in Table 2.

Table 2 Factor underlying ADRs reporting

Variables	Underreporting of ADRs	Motivators of ADR reporting	Remark
Unfamiliarity with ADR	√		ADRs training programs could improve reporting of ADRs
Unaware of ADR reporting policy and procedures	√		And awareness program
Low knowledge in ADR	√		And awareness program
Low level of encountering ADR	√		And awareness program
Low practice in ADR reporting	√		And awareness program
Diagnostic issues of ADRs	√		And awareness program
Suspected and trivial ADRs	√		And awareness program

Unaware of institute's ADR reporting systems	√		And awareness program
Unaware of ADR reporting forms	√		And awareness program
Unavailability of ADR reporting forms in the workplace	√		And awareness program
Lack of collaboration among professionals	√		And awareness program
Working in surgery	√		And awareness program
Lack of undergraduate training in ADRs	√		Incorporation of ADR training for undergraduates
Untrained patients regarding ADRs	√		-Do-
Lack of dietary supplements linked with ADRs	√		
Detecting ADRs and underreporting	√		Motivational strategies
Setting rules for disciplinary actions against defaulters	√		Creating stress and blame free culture
Compensation/rewards	√		Incentives
Positive attitude towards ADR reporting		√	
Training of professionals		√	
Life-threatening ADRs found in critical care and high awareness of ADRs		√	Requiring hospitalization or associated with fatality
Increasing age, reverse relationship between age and knowledge of ADR		√	Linked with high scores of ADRs awareness. sources
Higher qualification,		√	-Do-
A higher job position, Consultants detect and report ADRs more than specialists and resident doctors.		√	-Do- and specialists and resident doctors need intensive training in ADRs
More years of experience		√	-Do-
Hospital support for professionals			For attending ADRs training program
Enhanced awareness of ADRs reporting		√	-Do-
Blame free safe culture		√	

Awareness Program for ADRs

This program raises the awareness of health professionals regarding detection and reporting of ADRs to national PV system, regional centers in hospitals and competent health and regulatory authorities in Saudi healthcare settings. This program also informs professionals to be aware of the presence of ADR reporting policy in workplace and reminds them to read it thoroughly, and to know the process how to report ADRs. Besides, this program further informs them about the availability of forms used in ADRs reporting in workplace. In case forms are not available, the professionals should contact medication safety unit and quality assurance teams for their supply and in such scenario may report ADRs

verbally to professionals such as head of the department. To avoid this problem, quality or drug monitoring teams should check regularly for the availability of ADR reporting forms in healthcare departments, all wards, pharmacy, nursing stations, and emergency and ambulatory care services. Continuing medical education department in collaboration with ADR campaign program regularly organize seminars, workshops and lectures for updating professionals' information on ADRs in Saudi Arabia [4, 5]. In addition, this program provides guidance for searching important databases for relevant information on ADRs, and also evaluate that the professionals are satisfied with ADR information provided by the workplace. Finally, this program raises the awareness of professionals about internal ADR reporting and monitoring center and the external National Center of Pharmacovigilance at Saudi Food and Drug Authority (SFDA) and Ministry of Health. The Post-Marketing Surveillance PV is vital to the whole process used for monitoring and evaluating the ADRs [1, 50], and it is effective in preventing ADRs when these are reported spontaneously by physicians and allied professionals [50, 51]. ADRs monitoring requires a number of steps which are detection of ADR, causality assessment between drug and suspected ADR by using various algorithms, documentation of ADR in patient's medical file, and report of serious ADRs to pharmacovigilance or other related internal or external centers and drug regulatory authorities. For more detailed information of these steps, see this source [52].

ADRs Surveillance and Monitoring Program

ADRs surveillance and monitoring program was developed in Saudi Arabia using principles of pharmacovigilance (PV) which broadly involves all related sciences, practices and activities integrated to the detection, assessment, understanding and prevention of ADRs or any other drug related problems [1]. Vigilance and Crisis Management Executive Directorate is also concerned with detection, assessment and prevention of adverse drug reactions, and receives the ADR reporting through fax, internet, telephone and pre-paid mail. Besides spontaneous reporting system, post-marketing drug surveillance is reported to be done using several methods such as anecdotal reporting, intensive monitoring studies, prospective studies, case control studies, case cohort studies, medical record linkage studies, meta-analysis, and population statistics research [52]. Vigilance by clinicians (and patients) in detecting, diagnosing, and reporting ADRs is important for continuing drug safety monitoring [15]. Pirmohamed and colleagues suggested nine strategies including encouraging

professionals to report ADRs to regulatory agencies, identifying risk factors for different types of drug toxicity by using pharmacoepidemiological approaches, and detecting multiple genetic predisposing factors to allow the prediction of individual susceptibility for improving drug safety [15]. Furthermore, whereas in the context of vaccines Pillai suggested several epidemiological designs for pharmacovigilance especially focusing on randomization, placebo effect, ethical issues and validity of methods [53].

Pharmacovigilance in General

Pharmacovigilance is a powerful tool to detect signals of ADRs. PV also helps in assessing, analyzing and preventing ADRs. PV is defined as the practice of monitoring the effects of medical drugs after they have been licensed for use, especially in order to identify and evaluate ADRs reported post-marketing of drug, and often these reactions do not appear during phase I-III clinical trials (pre-marketing period). Another definition of PV is defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [1]. Pharmacovigilance, also known as drug safety, is the pharmacological science concerning the collection, detection, assessment, monitoring, and prevention of adverse effects of pharmaceutical products and devices. Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines [1-3]. Overall, PV prevents ADR and consequently ADEs. PV assesses and analyzes the spontaneously reported ADR during phase IV of drug post-marketing period. There is a need for global collaboration and partnership among stakeholders to develop diagnostic tools to further improve pharmacovigilance system.

PV system is an essential component of healthcare organizations worldwide because of many reasons. The collected clinical information about a medicinal product during its development phase is usually incomplete on account of a limited number of participants and the duration of clinical trials [3]. Moreover, phase I, II and III studies are done to establish the safety, toxicity, efficacy and side effect of newly developed drugs [3, 26]. The most common dose-related adverse drug reactions are usually detected in the pre-marketing phase [1]. Since most clinical trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medications suspected of developing interaction with the drug under study, the participants are not representative of the real world situations where the drug is eventually used [42]. The Phase IV clinical trial studies start when the drug is granted marketing license and its evaluation extends over many years. These post-marketing

pharmacoepidemiological studies evaluate extensively the effectiveness, safety, and utilization of the drug in larger, diverse populations in real-life conditions[54]. PV practices consistently help in early detection of ADRs. PV also facilitates in identifying both risk factors and the mechanisms underlying the ADRs. At the same time, PV system helps the healthcare agencies in taking precautions against future risks of medicinal products and recurrence of ADRs that are linked with large costs to public [3, 26,54]. Currently PV scope has grown to involve herbs, traditional and complementary medicine, blood products, biological and medical devices, vaccine, substandard and counterfeit medicines, medication errors and irrational use of medicine, and antimicrobial resistance[1]. Overall, as suboptimal reporting of ADRs is a worldwide phenomenon [36], detecting and reporting ADR to PV system is the responsibility of individual healthcare professionals including healthcare users for safe use of medicines[1-3].

Objectives of the Pharmacovigilance Center

Pharmacovigilance has multiple goals including developing pharmacoepidemiological trends of ADRs, estimation of quantitative aspects of benefit/risk analysis, dissemination of information needed to improve rational drug prescribing and proper regulation, develop strategies for rational and safe use of drugs and establishes communications and collaborations with international institutions having state-of-the-art experience in PV[42]. Kingdom of Saudi Arabia became an official member to participate in the WHO Program for International Drug Monitoring since 2009[55]. In accordance with the legislation, SFDA established a PV system for the collection and evaluation of information related to the risk-benefit ratio of medicinal products available in KSA, and monitors their safety profile. It takes appropriate action when necessary and monitors the compliance of The Marketing Authorization Holders and other related organizations linked with PV system. The SFDA ensures that these organizations implement management plans to effectively monitor and manage risks associated with the safety of their medicinal products. The PV activities in KSA come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the medicinal products under normal conditions of use in the market. PV obligations apply to all authorized medicinal products in KSA[56]. All frequent, minor to major serious ADRs occurring in all age groups including special populations, and are associated with old and new medications, vaccines, medical devices, withdrawal of

drugs, drug-drug interactions, herbal products or cosmetics, need to be reported to PV system and drug safety centers [42].

Pharmacovigilance in KSA

In 1998, the Ministry of Health (MoH) in KSA established post-marketing program that aims at early detection of unexpected and serious ADRs, epidemiological trend in known ADRs, and quality defect of registered products. This program publishes ADRs reports to disseminate data among healthcare professionals. Prior to conducting the training program, its course and objectives were announced in the main hospitals and private community pharmacies. In addition, ADR reporting form was distributed to these institutions to collect important information about ADRs and reporting system. Training program was carried out with the cooperation of the US FDA in the main 13 regions of KSA. Consequently, database from received ADR forms was constructed, and an advisory committee was established to study and classify the ADR reports. Although the training program targeted all healthcare professionals to report the ADRs, the response rate was limited [44].

To further consolidate the post-marketing pharmacovigilance, the Saudi Food and Drug Authority (SFDA) was established under the Council of Ministers resolution no (1) dated 07/01/1424 H. The SFDA is an independent body that directly reports to The President of Council of Ministers. The objective was to ensure safety of foods and drugs, biological and chemical substances, and electronic medical products. Once the FDA was fully functioning, the pharmacovigilance system was integrated with it. The SFDA has 4 main sectors including the drug sector which in coordination with different departments is responsible for protecting the public health in KSA [Figure 2]. The drug sector has a number of objectives [57]. It issues license for manufacturing, importing, and exporting, and the distribution, promotion and advertisement of medications. Drug sector assesses and monitors the safety, efficacy and quality of marketed medications, and gives marketing authorization certificate. It has a team of experts that inspects manufacturing units, importers, exporters, wholesalers and dispensers of medication products. It focuses on pharmacovigilance system. The drug sector is an independent information source on medications to healthcare professionals and the public, and also assures the safety of cosmetic products. It builds an effective relationship with the international drug authorities and scientific societies around the world. The drug sector organizes regularly short courses for health professionals and public for enhancing their health information and pharmaceutical care knowledge. It sets up the suitable rules, specifications and standards for drug's marketing authorization in the KSA. It monitors and follows the

marketed drug in order to observe its ADRs and prevents illegal marketing methods of medications [57]. Overall, it is wise to know that the rational use of medicines and patient safety are, but not limited to, the ultimate goal of pharmacovigilance [58].

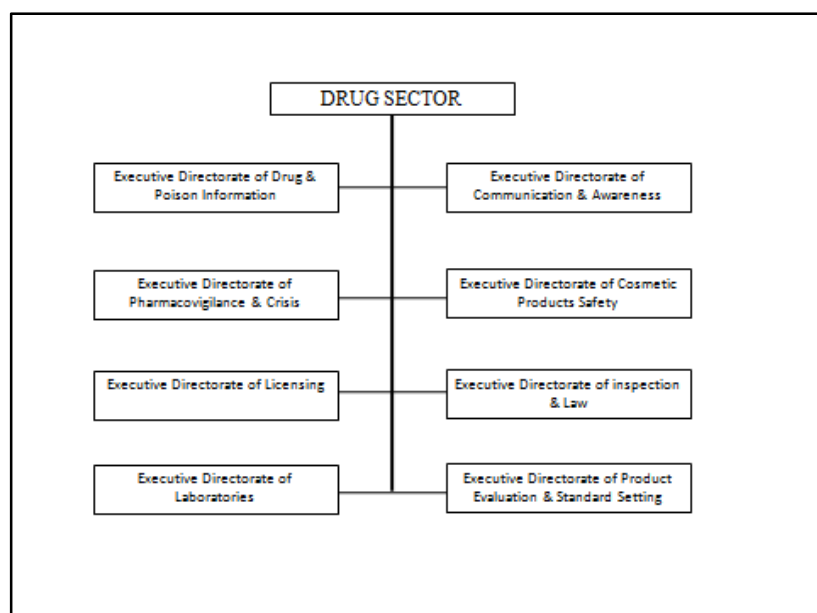


Figure 2: The Saudi Food and Drug Authority, Drug Sector Departments.

Discussion

Adverse drug reactions are important cause of morbidity and mortality around the world. Spontaneous reporting of these reactions is a fundamental part of successful Pharmacovigilance activities [1-3]. Unfortunately, unfamiliarity or unawareness with ADRs and their reporting procedures are major factors that lead to non-reporting of ADRs by professionals including pharmacists [4,5, 48,59]. Therefore, suboptimal reporting was found to be a common phenomenon globally. In several studies that explored KAAP of hospital physicians found that ADRs was underreported by those with low levels of awareness of policy and procedures, knowledge, and practice [4,5, 60,61], though they showed favorable attitude and willingness to improve their practice of ADR reporting, the latter was influenced by the job position and the knowledge score [48]. The low level of acquaintance with the institute's ADR reporting system and PV center and ADR forms varies from 25% to 47% across several studies [5, 62], and both factors are linked with ADR underreporting. The reporting of ADRs is a shared responsibility that need collaboration of all the team members

[4,5, 48], and similar findings were reported in a study [3] which suggested the contribution of all professionals including the nurses to the reporting of ADRs to pharmacovigilance.

Physicians working in critical care units had the highest ADRs awareness and ADRs reporting compared to those in surgical departments attributed to the differences in the settings and alertness, the types of patients, and the increasing number of medications used [43, 48,63]. The use of medications in surgical departments is often limited to antibiotics and pain killers, whereas in critical care or emergency departments a wide spectrum of medications is used [64]. Physicians with favorable attitudes, also influenced by place of work and culture of safety, fulfill their obligations to patient benefits by good quality reporting of ADRs to PV system [50, 65]. Surprisingly, physicians' high awareness of ADRs reporting is found to have reverse relationship with their attitude in critical care including emergency departments [66,67] attributed to high frequency of ADRs in such settings [5,48] and absence of clinical services provided by clinical pharmacists [67]. Similarly, detecting ADRs and practice of their reporting by physicians did not show direct relationship [62, 65] attributed to self image bias [68] together with inadequate and inappropriate reporting especially by verbal means [5]. The misconceptions related to the safety of drugs once in the market, and the confidentiality issues associated with ADRs reporting are some other factors underlying suboptimal reporting of ADRs to PV [4, 5, 48]. The underreporting and poor quality of ADR reporting are managed by using different strategies including decentralization of PV, educational interventions, lectures, development of alerts and monthly bulletins, scientific research, use of social networking, and extension projects [69]. Overall diverse factors underlie suboptimal reporting of ADRs to PV that negatively impact PV performance and patient safety.

Some studies suggested that the patients have a role in reporting ADRs and they need training in several areas including early detection and reporting of ADRs to PV and other reporting centers in hospitals [5, 48]. The training of patients is essential because they are reported to have limited awareness and knowledge of ADRs and reporting system, and about half of those who experienced ADRs have reported to their family physicians [70]. The implication of this finding is that the family physicians have a definite role in ADRs monitoring and reporting. In another study, patients expressed that reporting of ADRs is not their responsibility, and they need training to increase their awareness of ADRs and their reporting perspectives [71]. A randomized clinical trial that used an interactive educational program demonstrated the effectiveness of improving patients' reporting of ADRs [72]. The

role of patients in reporting ADRs remains controversial and possibly underestimated; nonetheless the reporting of ADRs by consumers tends to improve PV programs [73]. Other researchers stated that reporting of ADRs by consumers tends to increase the rate of ADR reporting to [8, 74] and reliability of PV system [75]. In another study, Härmark and colleagues reported three key points concerning patient-reported drug safety information that adds value to pharmacovigilance signal detection, and leads to better understanding of the patient's experiences of the ADR. Furthermore, pharmacovigilance needs to develop patient-specific form, development of a severity grading and evolution of the database in order to make use of patients reported ADR information [76]. In a nutshell, the reporting of ADRs by healthcare users is a true reflection of their real experiences.

Several studies have reported a number of motivating and hindering factors underlying ADRs reporting to PV centers [5, 48, 68]. The low awareness of ADRs reporting system is another reason for ADRs underreporting [68], and this finding is inconsistent with the results of other study in which more than 80% of the physicians were aware of the system, and yet underreported ADRs [5]. The literature provides strong evidence of improvement in attitudes towards ADR reporting by various types of interventions such as skill-based training [46], self-training aided by educational tools [65], and on job educational programs supported by handouts [77]. The physicians' awareness of ADR detection and reporting influenced by the feeling of being adequately trained underscore the importance of CME in improving their KAAP towards ADR and PV [36, 48, 65, 77, 78]. Similarly, the undergraduate training in PV needs to be sufficiently delivered to physicians who are involved in ADR monitoring and reporting in their future career [8]. Arguably, continuous training of professionals including community pharmacists in ADRs reporting to PV needs to be mandatory in all general hospitals around the world [68, 79]. Community pharmacists tend to report ADRs to physicians rather than to PV center [59] and, therefore, a strong link need to be developed between health professionals and community pharmacists. Overall continuing training of health professionals in ADR need to a global agenda as it is linked to optimal, quality reporting of ADRs to pharmacovigilance that ensures patient safety.

Pharmacovigilance, an essential tool for patient and public safety [80] detects adverse effects of pharmaceutical products not identified during clinical trials conducted pre-marketing period. These ADRs are rare but potentially important from the perspective of patient safety. In other words, post-marketing drug surveillance is complementary to the pre-marketing identification of most frequent ADRs of newer drugs. However, most ADRs need

to be reported spontaneously to the PV by professionals in health settings, drug industries and patients. Most importantly pharmacovigilance needs to be patient focused [76]. As underreporting of ADRs adversely affects the functioning of pharmacovigilance [81], and, hence, optimal reporting of ADRs needs to be achieved. This is important because PV analyses these reactions and provide immediate solutions to prevent ADRs and ensures patient safety. Roux et al (2005) developed a practical approach for evaluating automatic signal generation methods implicitly involved the human, material, and time resources available for interpreting and exploiting retrieved information. Moreover, this approach should be adopted not only for evaluating measures of association, but also for developing new measures [81]. Validated data collected in pharmacovigilance system on ADRs using mining techniques such as Multi-item Gamma Poisson Shrinker [82] have other clinical applications including identification of higher-than-expected reporting relationships between drugs and events [83], detection of delayed toxicity of concomitant drug such as antipsychotics induced pancreatitis and diabetes mellitus [82], and assisting drug regulatory functions in terms of safety warnings, changes of product information, suspension or withdrawal of drug license [58]. Pharmacovigilance centers also alert prescribers, manufacturers and the public to new risks of ADRs. Pharmacovigilance is now considered a medical science. Furthermore, pharmacovigilance archived data from International Pharmacovigilance Agency (WHO database, VigiBase™) could be used to study the rare syndromes such as Kounis Syndrome in which symptoms of cardiovascular system (acute coronary syndrome and myocardial infarction) and allergy occur concurrently and often patient dies of acute cardiovascular disease [84]. Pharmacovigilance system may also help in identification of ADRs globally and risks of self-medications provided related ADRs are reported spontaneously to PV [85]. Overall, pharmacovigilance fairly contributes to the safe use of medicinal products and devices globally; however there remain many challenges including priority to pharmacovigilance development and good pharmacovigilance practice in the Eastern world [86,87].

Conclusion

Adverse drug events including adverse drug reactions cause significant mortality and morbidity around the world. Although several reports have clarified the confusion concerning the terminology of ADRs and related terms, a large number of factors underlying poor quality reporting of ADRs and their underreporting are perceived to be the major challenges that pharmacovigilance faces in current circumstances. The role of healthcare professionals and

patients is to report all serious ADRs spontaneously and qualitatively to pharmacovigilance that helps early signal detection leading to safe use of drugs and, thus, ensures patient safety and reduction in public health burden.

Conflicts of Interest: None

Ethical Consideration: Not applicable

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