Review Article

Overview of Adverse Drug Reactions: Classification, Reporting, Prevention, and Role of Pharmacist

Deepthi Gangula[a,#], Sheetal Kshirsagar[a,#], Sudheer K Dundigalla[b], Satyanarayana SV Padi[a,c,*]
[a] Department of Pharmacy Practice, Care College of Pharmacy, Kakatiya University, Hanamkonda, TG, India.
[b] Department of Pharmaceutics, Care College of Pharmacy, Kakatiya University, Hanamkonda, TG, India.
[c] Department of Pharmacology, Care College of Pharmacy, Kakatiya University, Hanamkonda, TG, India.
***Corresponding author's E-mail:** ssvpadi@gmail.com

Received: 25-05-2024; **Revised:** 28-08-2024; **Accepted:** 12-09-2024; **Published on:** 15-09-2024.

ABSTRACT

Adverse drug reactions (ADRs) are one of the leading causes of morbidity and mortality in healthcare. An ADR occurs when healthcare service is provided and a safety issue arises whenever therapeutic choices have to be made. Therefore, the classification, identification, assessment, reporting, prevention (prophylactically), and pharmacological and non-pharmacological management of an ADR has become an important aspect of drug therapy. In addition, establishing drug safety, pharmacovigilance, drug utilization and evaluation, and surveillance programs helps fulfill key elements of ADR reporting. Furthermore, the skilled services of clinical and community pharmacists, are essential in the development and execution of ADR reporting programs in their practice along with pharmacists' role in educating and promoting awareness of ADR to the public can save lives. This review article briefly summarizes the key elements of correctly defining, classifying (type), and reporting elements of an ADR, and preventive strategies in managing an ADR. Further, it summarizes the role of a pharmacist in participating in ADR surveillance programs, monitoring, identifying, and reporting an ADR that can help determine its management and future therapeutic choices.

Keywords: ADR, ADR Reporting, Adverse drug reactions, DoTs, Pharmacovigilance, PvPI, Vigiflow, Yellow card scheme.

INTRODUCTION

An adverse drug reaction (ADR) can be defined as "A noticeably harmful or unpleasant reaction resulting from an intervention related to the use of the medicinal product".[1] The definition states that an adverse effect usually predicts hazard from future administration, warrants prevention, specifies a treatment approach, alters the dosage regimen, or withdraws the administration of the drug product.[2] Since 2012, the definition has expanded to include not only the authorized use of a medicinal product in normal dosages but also the reactions that may arise from medication errors, drug calculation and administration mistakes, abuse, or misuse as well as suspected reactions to unlicensed or off-label medications.[3]

Researching ADRs in terms of early detection and prevention as well as encouraging medical professionals to report ADRs are essential to reducing the severity of undesired, unexpected, and harmful effects and the cost of treatment and rehospitalization due to a potential ADR[4]**.** A World Health Organization (WHO) report states that about 60% of ADRs can be avoided by rationalizing drug selection and prescribing practices.[3,4] Widespread polypharmacy has resulted from the rising number of patients with multimorbidity and the complexity of therapeutic agents, which could lead to an increase in potential drug-drug interactions (pDDIs), particularly in the elderly. Notably, DDIs, inappropriate dosage, and inadequate monitoring are the most common factors influencing the preventability of ADRs.[2-4] Indeed, patient demographics (gender and age) and ADR characteristics (drug type, ADR type, system organ category, outcome, management, de-challenge/re-challenge, and reporter status) have been used to categorize the ADRs.[2-5]

1. CLASSIFICATION OF ADVERSE DRUG REACTIONS

1A) ABCDE Classification: An ADR is frequently classified as a 'type A' and 'type B' reaction but later other classes have also been added.[1]

a) Type A (Augmented) reactions: These are due to the exaggeration of normal pharmacological effects of the drug at a usual therapeutic dose and are usually dose-dependent. These effects occur frequently, are predictable, and are associated with low mortality rates.[1] Examples include (1) Opioids induce respiratory depression[6] or warfarin bleeding[7], (2) drug-induced liver damage is a well-known kind of type A reaction that may be caused by an overdose of acetaminophen[8], (3) phototoxicity and yellowing of teeth due to tetracycline exposure[9], nephrotoxicity caused by aminoglycosides[10], and (4) digestive facet effects, such as erosive gastritis, peptic ulcer disease, bleeding ulcers secondary to NSAID therapy.[11] Type A reactions also include those that are not directly related to the desired pharmacological action of the drug, such as dry mouth that is associated with tricyclic antidepressants.[12]

b) Type B (Bizarre) reactions: These are new reactions that are not anticipated from the direct pharmacological outcomes of the drug. These are much less frequent, not unusual, and might consequently be found for the first time after a drug has been administered for its preferred use. Examples include (1) hypersensitivity reactions like

anaphylaxis to beta-lactam antibiotics, such as penicillins and cephalosporins[13], (2) idiosyncratic reactions like malignant hyperthermia with anaesthetics[14], (3) intolerance reactions or low tolerance threshold to drugs (beta-lactams, macrolide, tetracyclines, anti-HIV drugs, and anticancer antibiotics and tyrosine kinase inhibitors)[15], (4) idiosyncratic reactions, such as a drug-induced liver injury due to carbamazepine, felbamate, isoniazid, infliximab[16], (5) immune-mediated (allergic) reactions due to penicillins, fluoroquinolones, vancomycin, curare mimetics[17,18], (6) chloramphenicol-induced aplastic anaemia[19], and (7) rifampicin- and isoniazid-induced hepatitis[16,20].

c) Type C (Continuing) reactions: These ADRs persist for a prolonged time after their incidence. Examples include (1) the use of bisphosphonates resulting in osteonecrosis of the jaw[21] and (2) hypothalamic–pituitary–adrenal axis suppression by corticosteroids[22].

d) Type D (Delayed) reactions: These ADRs remarkably appear slowly a while after the usage of the drug. Additionally, the timing of those can also make them too hard to detect. Examples include (1) leucopenia could arise up to 6 weeks after a dose of lomustine[23], (2) tardive dyskinesia, a late form of extrapyramidal side effect of first-generation antipsychotic agents[24], (3) teratogenesis due to typical antiepileptics (fetal hydantoin syndrome)[25], and (4) carcinogenesis due to immunosuppressants[26].

e) Type E (End-of-use) reactions: These are due to the sudden withdrawal of a drug. Examples include (1) insomnia, tension, and perceptual disturbances following the withdrawal of benzodiazepines[27], (2) myocardial ischemia after β-blocker discontinuation[28], and (3) withdrawal syndrome with opiates or benzodiazepines[27,29].

f) Type F (Failure of therapy) reactions: These ADRs are due to unexpected failure of therapy, where a drug undesirably increases or decreases in efficacy. Examples include (1) the decreased clearance of a drug by dialysis and plasmapheresis[30,31], (2) the decreased efficacy of a drug because of drug interactions altering metabolism[32,33], (3) the effects of critical illness on protein binding and elimination[34,35], and (4) the decreased effect of antibiotics (Meropenem, Linezolid, and Colistin, penicillin, cephalosporins, fluoroquinolones, macrolides) due to resistance[36-38].

1B) DoTS (Dose, Timing, Susceptibility) Classification: This three-dimensional classification system is based on essential considerations of dose-associated, time-associated, and patient susceptibility factors.[39]

a) Dose relatedness: The risk and severity of these ADRs are directly related to the administered drug(s), its pharmacological action and class, and the dose(s) administered. Examples include (1) immunogenic response to hepatitis B vaccine[40], (2) type IV hypersensitivity skin reactions, such as allergic contact dermatitis, Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN))[41,42], and (3) cephalosporins desensitization by the use of increasing doses of drug (antigen)[43].

b) Time relatedness: These types of ADRs occur either time-independent or depend on the timing of the first and multiple doses of the drug. **(I) *Time-independent reactions*** include (1) digoxin toxicity when the patient's renal function worsens[44] and (2) digoxin toxicity in association with potassium depletion[45]. **(II) *Time-dependent reactions*** are divided into six subtypes, viz., rapid, first dose, early, intermediate, late, and delayed. Examples of **(i) rapid ADRs** include red man syndrome with vancomycin (vancomycin flushing reaction)[46], **(ii) first dose ADRs** include (1) hypotension after the first dose of an angiotensin-converting enzyme (ACE) inhibitor[47], (2) anaphylaxis to pencillins[13,17], and **(iii) early reaction ADRs** include nitrates-induced headache[48]. The ADRs of **(iv) intermediate reaction** include (1) thrombocytopenia due to quinine, quinidine, rifampicin, abciximab, carbamazepine, ceftriaxone, eptifibatide, suramin, heparin, trimethoprim-sulfamethoxazole, ibuprofen, mirtazapine, oxaliplatin, penicillin, tirofiban, and vancomycin [49], (2) interstitial nephritis with penicillins[50], (3) cutaneous hypersensitivity (urticaria and angioedema) to antihistamines[51], and (4) ampicillin/amoxicillin pseudo allergic rash[13,17,52]. The ADRs of **(v) late reactions** include (1) tardive dyskinesia with first-generation antipsychotics (dopamine receptor antagonists)[24] (2) opiate and benzodiazepine withdrawal syndromes[27,29], (3) hypertension after withdrawal of clonidine or methyldopa[53,54], and (4) acute myocardial infarction after withdrawal of beta-blockers[28]. The ADRs of **(vi) delayed reactions** include (1) carcinogenesis (vaginal adenocarcinoma in women who were exposed to diethylstilbestrol in utero[55], (2) teratogenesis, such as phocomelia due to thalidomide[56].

c) Patient susceptibility factors: Various factors, such as age, gender, altered physiology, genetic, and exogenous origin make patients susceptible to incidence and increased severity of ADRs. **(I) Age susceptible** ADRs include (i) chloramphenicol-associated grey baby syndrome in neonates[57] and (ii) extensive sleep pattern disturbances due to hypnotics in the elderly[58]. **(II) Gender predominant**, but not limited, susceptible ADRs include increased prevalence of (i) alcohol intoxication[59], (ii) mefloquine-neuropsychiatric effects[60], (iii) ACE Inhibitors-cough[61], and (iv) drug (ethosuximide, secukinumab, procainamide, hydralazine, sulfasalazine, isoniazid, and carbamazepine)-induced lupus-like syndrome in females[62]. The examples of ADRs with **(III) altered physiology** include the risk of teratologic effects associated with the use of antiepileptics, such as valproate, phenobarbital, phenytoin, carbamazepine, and lamotrigine in pregnancy[25,63]. The ADRs due to **(IV) genetic changes** include (i) drug-induced pseudoporphyria due to various drugs (NSAIDs, antibiotics, retinoids, diuretics, and oral contraceptives)[64], (ii) succinylcholine sensitivity[65], (iii) malignant hyperthermia[66], and (iv) CYP isoenzyme

polymorphysisms[33]. Certain ADRs are due to **(V) Exogenous factors**, such as drug interactions with (i) grapefruit juice (food) wherein these drugs cleared by CYP3A4[67,68] and (ii) diseases including (a) renal insufficiency and increased lithium toxicity[69] and (b) hepatic cirrhosis and morphine-induced hepatic encephalopathy[70].

d) Description of an 'ADR' based on the DoTS (Dose-Time-Susceptibility) classification[71]

(i) Osteoporosis due to long-term use of corticosteroids in pediatrics, adults, women of childbearing age, post-menopausal women, and risk populations.[72] **Do**: collateral effect; **T**: late; **S**: age, gender.

(ii) Anaphylaxis due to penicillin.[13,17,73] Do**:** hypersusceptibility; **T**: first dose; **S:** not understood, needs previous sensitization.

(iii) Hepatotoxicity because of isoniazid.[16,20,74] **Do:** collateral effect; **T**: intermediate; **S**: genetic (drug metabolism), age, exogenous (alcohol), sickness (malnutrition).

2. REPORTING OF 'ADRs' – STANDARDS AND SYSTEMS

Reports of ADRs are usually initiated by healthcare staff such as general physicians (GP), GP associates, pharmacists, nurses, or drug safety directors from hospitals, ambulatory sites, or communities.[75,76] Reporting systems might also be designed to receive reports from patients, families, or client advocates. Reporting might capture errors, injuries, non-harmful errors, instrumentation malfunctions, method failures, or alternative hazards.[77] While an individual report might contain necessary info about a specific incident or event, the notion of a reporting system refers to the processes and technology concerned within the standardization, communication, formatting, feedback, evaluation, learning, response, and dissemination of lessons learned from reported events.[75,77,78]

ADR susceptibility is impacted by factors such as pregnancy, quality, polypharmacy, disease states, age, and gender.[76,77,79] Drug safety depends on nurses and other medical professionals being aware of the potential for ADRs, collaborating with patients to maximize medication use, and being watchful when reporting ADRs via the Yellow Card Scheme[80]."The science and activities reference with the detection, assessment, understanding, and interception of adverse effects or any other possible drug-related problem, particularly long-term and short-term adverse effects of medicines," is how the WHO defines pharmacovigilance.[77,78,81] Throughout the past 50 years, spontaneous reporting systems, such as the UK's Yellow Card Scheme, were established in 1964 following the thalidomide disaster of the 1950s. Through spontaneous reporting, the scheme collects information on suspected ADRs for both licensed and unlicensed medicines and vaccines, including those purchased over the counter or by prescription. validation of a report requires only four items of data, namely (i) an identifiable patient, (ii) a reaction, (iii) a suspected medicinal product, and (iv) an identifiable reporter. Therefore, reporters are encouraged to provide as much detailed information as possible to provide additional data and clinical context for assessors.[82]

Although frequently used for pharmacovigilance, spontaneous reporting systems function effectively when adverse events are uncommon and unusual (affecting fewer than 1% of treated patients) and when an event indicates a condition brought on by the drug (such as erythema multiforme).[75,76,81] Their use is more confined to identifying a small increase in the rate of common events, such as myocardial infarction or stroke. This is the reason why recent drug safety scandals, such as thiazolidinedione-induced and rofecoxib-induced cardiovascular events, remained undetected despite the widespread use of these agents.[81-83] Reporting is further impacted by ignorance about where and how ADRs should be reported. Lack of time or overload, legal considerations, ignorance (that only serious ADRs are to be reported), fear that intense ADRs are already documented once a drug is introduced into the market, and financial incentives are other potential causes of poor reporting.[82-85] Importantly, four main obstacles to the reportage of ADRs have been recognized, such as (i) pharmacovigilance is seen as an improbable ideal, (ii) the reportage authority is perceived as a virtual and remote entity, (iii) healthcare professionals don't feel involved in the risks related to the medications utilized in their practice, and (iv) Healthcare professionals are unsure regarding the scope of their role in reporting adverse effects.[86-89]

3. STRATEGIES TO IMPROVE REPORTING OF 'ADRs'

Reporting of ADRs is generally done by medically educated and professionally certified, qualified, or licensed/ registered healthcare practitioners (clinicians, dentists, pharmacists, nurses) who are skilled and trained to collect, validate, summarize, and analyze ADRs.[75,90-92] Moreover, patients and consumers are also inspired to report and acknowledge ADRs to prevent similar suffering in other patients, prevent future incidents, minimize the risk, reduce the incidence of ADRs, avoid hospitalization, and reduce the cost of treatment and economic burden on their families and societies. Indeed, patients and their family members are encouraged to extend their familiarity with reportage processes to enhance the quality and quantity of reporting.[92-94] However, it has been reported that patients might not be aware of ADR reportage systems and may be confused about how and where to report.[90,95-97] Numerous strategies have been implemented to improve the knowledge, attitude, and practice of ADR reporting. The first is to improve patients' knowledge, attitudes, and practice toward the reportage of ADRs as there is a need for public awareness campaigns to deal with the importance of reporting.[78,79,97,98] Second, by providing feedback to patients with their reportage followed by assessment of patients reporting in a higher

cognitive process, comparison of the results of reports, and enhancement of patient awareness on ADRs and reporting management systems. [89,90,93,97] Third, to design a single or unique official reporting system for each patient and healthcare provider, to develop measures to enhance the interfacing of patients' and healthcare providers' reports, and to process and evaluate the potential ADRs within the bulk data of similar reports.[79,90,97,98] In addition, all healthcare providers including pharmacists and nurses who spend the most time with patients and collect knowledge on patients' bedside conditions should be educated on the way to participate in reporting ADRs as the large data of ADR reports will improve the impact of the pharmacovigilance system.[79,90,99]

4. ESSENTIAL CHARACTERISTICS OF A GOOD QUALITY 'ADR' REPORT

The minimum criteria for reporting ADRs for the regulatory body requirements, and the essential characteristics and the required data components for an ADR case are (i) a recognizable reporter, (ii) an identifiable patient, (iii) an adverse reaction, and (iv) a suspect product[71]. Some barriers to the effective implementation of the ADR reporting and observance system might be money constraints, the absence of clinical confirmation of patients' reports, the impossibility of sharing patients' reports with primary healthcare suppliers, and the inability to match reports from totally different sources. Mechanisms for reporting and recording ADRs must not solely provide info regarding the entire variety of reports but also add their severity, unexpectedness, and therefore the degree of causality attributed to ADRs.[90,95-97,100]

5. ANALYSIS AND CAUSALITY ASSESSMENT OF REPORTED ADRs

ADR reporting is important for drug safety analysis within the post-marketing phase. It is an ongoing and continuous method. Studies from the institute help to spot and rectify the issues associated with ADR reporting. Reporting adverse drug reactions (ADRs) is undoubtedly hampered by several factors, including polypharmacy, difficulty detecting ADRs, physician workload, and time constraints.[99-102] Essentially, the data on the ADRs should be analyzed and evaluated considering numerous parameters, such as (i) patient characteristics, particularly age, gender, health status, organ function status, co-morbidities, past and current medication history, and previous known allergies and events of ADR[103-105], (ii) ADR characteristics including individual reactions, ADR type, class, and affected organ system[90,100,101], (iii) drug characteristics including the name of the drug, dose (amount, single and multiple), route, time, and rate of administration, brand and generic names, manufacturing and labelling information, and therapeutic and pharmacological class[105,106], (iv) causality assessment using the validated scale, such as the Naranjo Probability scale as definite, probable, and possible[104-106], (v) severity assessment to categorize ADR into mild, moderate, and severe based on their severity with the help of severity assessment criteria developed by Hartwig et al.[104-106], (vi) outcome assessment of patient experienced ADR for recovery and survival, such as totally recovered, recovered, unknown, or fatal[103-106], (vii) management of ADR including the abatement of a drug, substitution of the drug, dose reduction, rechallenge, dechallenge, extra intervention for ADR, any changes in management plan, or no further treatment[101,104,106-108]. Considering the requirements to promote awareness, encourage reporting, and educate causality assessment of ADR amongst healthcare professionals, steps should be taken to reassure and improve the quality of ADR reporting by organizing seminars and workshops for clinicians and paramedical staff.[100,102,109]

6. ADR REPORTING IN INDIA

A common standardized data set characterized by quality, comparability, and reporting rates will optimize drug safety surveillance efforts. Moreover, regulation at the system level desires the inclusion of comprehensive, systematic, and regular patient checking for undesirable adverse effects of medicines. The Pharmacovigilance Programme of India (PvPI) is an initiative by the Central Drugs Standard Control Organization (CDSCO) in collaboration with the Indian Pharmacopoeia Commission (IPC), operating under the Ministry of Health and Family Welfare, Government of India.[79,90-94,100,110,111]

6A) What to report: Regardless of a proven causative link between a medicine and any suspected ADR, the PvPI supports the reporting of all suspected ADRs, regardless of whether they are known, unknown, significant, non-serious, common, or rare.[90,91,94,110]

6B) Where to report: Patients and consumers and all medical professionals, such as dentists, pharmacists, nurses, and clinicians will report ADRs to the National Coordination Center (NCC) or ADR Monitoring Centre (AMC). Pharma companies may also provide NCC-specific case safety reports related to their products.[90,91,94,110]

6C) How to report: Suspected ADR reporting forms for healthcare professionals and customers are accessible on the website of IPC to report ADR. To remove the language barrier in ADR reportage, the customer reporting form is made accessible in ten vernacular languages (Hindi, Tamil, Telugu, Kannada, Bengali, Gujarati, Assamese, Marathi, Oriya, and Malayalam). On weekdays from 9:00 am to 5:30 pm, ADRs are frequently additionally reported by calling the PvPI support number (18001803024).[90,91,94,110]

6D) Whom to report: A reporter will send the filled ADR reporting form directly to NCC or their nearest AMC. Just in the case of AMC, these reports are confirmed by care professionals entered into Vigiflow, and sent to NCC for more assessment. These reports are finally assessed at the NCC and carried out at the WHO-Uppsala Monitoring Centre. The obtained data is entered within the drug safety database, analyzed, and assessed by the specialists to spot new signals.[90,91,94,110]

The submitted ADR reports do not have any legal implications for the reporters as the patients' identities are held in strict confidence and guarded to the fullest extent. Therefore, healthcare providers are inspired to report ADRs for a higher understanding of the risks related to the utilization of medicines and to safeguard the health of the Indian population.[91,94,104]

7. PREVENTION OF AN ADVERSE DRUG REACTION

Preventing ADRs depends on avoiding treatment in cohorts of patients who are at risk, enhanced susceptibility, or providing treatment reduces the danger of an adverse effect (e.g. co-administration of different medicines, observation of biopsy results). Spontaneous reportage (using the Yellow Card Scheme within the UK) supported the suspicion that an ADR is an essential part of pharmacovigilance studies; however, ADRs are immensely underreported across tending healthcare settings and sectors. If unsure, it is best to submit a report.[77,78,81,82] Besides, ADRs are one of the great mimics in healthcare, typically emulating 'traditional diseases' and manifesting in all systems of the body. Drug-related issues in patients admitted to a hospital could be different in various ways, such as weakness or somnolence, biochemical or hematological derangements (such as urinary organ injury, electrolyte imbalance or anemia), bleeding, gastrointestinal disturbances, hypoglycemia[79-82,112,113], age groups and special populations (pediatrics, pregnants, geriatrics)[114-116], irrational prescribing and use of antibiotics and loss of effectiveness due to antibiotic resistance[9,38,117,118], drug-related urgent hospitalizations[119,120], drug-related readmission[121,122], or healthcare-associated infections, such as Clostridia difficile infection[38,109, 122-124].

Two basic steps will be followed to prevent an ADR from occurring. First, identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment alternative consequently. Second, ensure the treatment plan mitigates any potential adverse effects. Apart from this strategy, healthcare practitioners should (i) avoid and be vigilant of high-risk drugs[114,116,125], (ii) discontinue unnecessary drugs and irrational use of drugs[119,136,127], (iii) consider drugs as a cause of any new symptom[9,116,127], (iv) identify irrational use (misuse, underdose, overdose, drug abuse, over the counter use, self-medication)[116,118,120,15], (v) identify the wrong route of administration[114,116,122], (vi) identify co-administration of multiple drugs, drugs of the same therapeutic class, and alcohol[125,126], (vii) avoid treating side effects with another drug leading to unnecessary use of irrelevant dose and inappropriate drugs[9,126-128], (viii) identify and avoid potential risk of drug-drug interactions[114,119], (ix) adjust dosing based on age, the status of liver and kidney function, and mineral ion balance[38,122,125] (x) risk/benefit consideration, and management plan[111,125,129], (xi) investigate the problem's cause, action and follow-up[116,122], (xii) identify barriers to medication adherence and address medication non-adherence[126,127], (xiii) educate patients and family members to seek medical services, get to know medical emergency contact numbers and personnels, and bring to medical attention on experiencing undesired effects after drug administration[119,126,130], (xiv) update continuously on pharmacogenetics, evidenced based practice guidelines, and latest ADR signals from clinical trials[131-133], and (xv) promoting and improving patient awareness of rational use of drugs, and avoiding and management of ADRs[117,118,128-130].

8. ROLE OF PHARMACIST IN REPORTING AND MANAGING ADRs

A patient's primary point of contact with the healthcare system both before and throughout drug therapy is a pharmacist. ADRs in health systems can be better designed and implemented with the assistance of pharmacists, who are particularly suited to offer useful information about medication products, monitor adverse events, and assist in designing and implementing system improvements.[87,88,134] Emphatically, pharmacists play a quintessential role pivotal to identifying, assessing, strategically planning management, resolving, and preventing ADRs, and can be further enhanced through education and training of one's self as well as patients.[86-89] Notwithstanding this, it is equally important to emphasize the importance of regularly monitoring and reporting ADRs, particularly among clinical and community pharmacists.

The pharmacist should facilitate the following activities, such as (i) analyzing each reported ADR, (ii) identifying drugs and patients at high risk associated with ADRs and adverse events, (iii) the development of scope, policies, and procedures for the ADR monitoring and reporting programs, (iv) description of the responsibilities and interactions of pharmacists with clinicians, nurses, risk managers, and other healthcare professionals in the ADR programs, (v) making academic and promoting self- and patients' educational use of the ADR programs, and (vi) collecting appropriate data to create, preserve, and regularly assess ADR records and databases including use of uniform reporting rates and tracking the frequency of ADR incidents regionally, nationally, and globally, (vii) sharing information to regulatory authorities and public health departments nationally and globally, (viii) application of data acquired by the ADR program in signal detection and evaluation, (ix) creating and managing databases throughout the organization and across the nations, (x) developing risk evaluation, mitigation and minimization strategies, (xi) promoting awareness and education on rational drug use and ADRs, and (xii) facilitating the reporting of serious or unexpected ADRs[86-89,131-136].

SUMMARY

Owing to the paramount importance of monitoring, managing, and preventing ADRs in assuring health benefits, improving trust in drug regulatory authorities, gaining acceptance of new drug approvals, promoting

rational drug use, minimizing drug resistance and treatment failure, and enhancing drug safety to patients, special emphasis should be given in understanding ADR classification, dose, types, susceptibility, and associated risk factors in identifying and reporting an ADR. The overall objective of lowering the risk and severity of ADRs within a clinical setting should be attained by programs that prioritize surveillance, thorough documentation in medical records, reporting to and evaluation by an interdisciplinary committee, and healthcare providers' and patients' education. Progressively, clinical and community pharmacists can help with the coordination and intercommunication between clinicians and patients of ADR reporting programs.

Ethical approval: Not required

Disclaimer (Artificial intelligence): Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259. doi:10.1016/S0140-6736(00)02799-9
2. Wolf U, Baust H, Neef R, Steinke T. Individual Pharmacotherapy Management (IPM)-IV: Optimized Usage of Approved Antimicrobials Addressing Under-Recognized Adverse Drug Reactions and Drug-Drug Interactions in Polypharmacy. Antibiotics (Basel). 2022;11(10):1381. doi:10.3390/antibiotics11101381
3. López-Valverde L, Domènech È, Roguera M, Gich I, Farré M, Rodrigo C, et al. Spontaneous Reporting of Adverse Drug Reactions in a Pediatric Population in a Tertiary Hospital. J Clin Med. 2021;10(23):5531. doi:10.3390/jcm10235531
4. Shchory MP, Goldstein LH, Arcavi L, Shihmanter R, Berkovitch M, Levy A. Increasing adverse drug reaction reporting-How can we do better?. PLoS One. 2020;15(8):e0235591. doi:10.1371/journal.pone.0235591
5. Jiang H, Lin Y, Ren W, Fang Z, Liu Y, Tan X, et al. Adverse drug reactions and correlations with drug-drug interactions: A retrospective study of reports from 2011 to 2020. Front Pharmacol. 2022 Aug 22;13:923939. doi: 10.3389/fphar.2022.923939.
6. Palkovic B, Marchenko V, Zuperku EJ, Stuth EAE, Stucke AG. Multi-Level Regulation of Opioid-Induced Respiratory Depression. Physiology (Bethesda). 2020;35(6):391-404. doi:10.1152/physiol.00015.2020
7. Ozturk M, Ipekci A, Kiyak SK, Akdeniz YS, Aydin Y, Ikizceli I, et al. Bleeding Complications in Warfarin-Treated Patients Admitted to the Emergency Department. J Clin Med Res. 2019 Feb;11(2):106-113. doi: 10.14740/jocmr3669.
8. Liao J, Lu Q, Li Z, Li J, Zhao Q, Li J. Acetaminophen-induced liver injury: Molecular mechanism and treatments from natural products. Front Pharmacol. 2023 Mar 27;14:1122632. doi: 10.3389/fphar.2023.1122632.
9. Jetty P, Gaddam S, Padi SSV. Emergence of Third Generation Tetracyclines: New Magic Bullets to Tackle Antibiotic Resistance in the Post-Antibiotic Era". Asian J Res Infect Dis. 2023;13(4):1-14. https://doi.org/10.9734/ajrid/2023/v13i4271.
10. Chou CL, Chuang NC, Chiu HW, Liao CT, Hsu YH, Chang TH. Aminoglycosides use has a risk of acute kidney injury in patients without prior chronic kidney disease. Sci Rep. 2022 Oct 14;12(1):17212. doi: 10.1038/s41598-022-21074-x.
11. McEvoy L, Carr DF, Pirmohamed M. Pharmacogenomics of NSAID-Induced Upper Gastrointestinal Toxicity. Front Pharmacol. 2021;12:684162. doi:10.3389/fphar.2021.684162
12. Teoh CXW, Thng M, Lau S, Taing MW, Chaw SY, Siskind D, et al. Dry mouth effects from drugs used for depression, anxiety, schizophrenia and bipolar mood disorder in adults: systematic review. BJPsych Open. 2023 Mar 20;9(2):e53. doi: 10.1192/bjo.2023.15.
13. Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the Frequency of Dual Allergy to Penicillins and Cefazolin: A Systematic Review and Meta-analysis. JAMA Surg. 2021 Apr 1;156(4):e210021. doi: 10.1001/jamasurg.2021.0021.
14. Hopkins PM, Girard T, Dalay S, Jenkins B, Thacker A, Patteril M, McGrady E. Malignant hyperthermia 2020: Guideline from the Association of Anaesthetists. Anaesthesia. 2021 May;76(5):655-664. doi: 10.1111/anae.15317.
15. Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. J Allergy Clin Immunol Pract. 2020 Oct;8(9S):S16-S116. doi: 10.1016/j.jaip.2020.08.006.
16. Uetrecht J. Idiosyncratic Drug Reactions: A 35-Year Chemical Research in Toxicology Perspective. Chem Res Toxicol. 2022;35(10):1649-1654. doi:10.1021/acs.chemrestox.2c00090
17. Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. Allergy. 2019 Aug;74(8):1457-1471. doi: 10.1111/all.13765.
18. Han J, Pan C, Tang X, Li Q, Zhu Y, Zhang Y, Liang A. Hypersensitivity reactions to small molecule drugs. Front Immunol. 2022 Nov 10;13:1016730. doi: 10.3389/fimmu.2022.1016730.
19. Andaluz-Scher L, Medow NB. Chloramphenicol Eye Drops: An Old Dog in a New House. Ophthalmology. 2020 Oct;127(10):1289-1291. doi: 10.1016/j.ophtha.2020.05.015.
20. Zhuang X, Li L, Liu T, Zhang R, Yang P, Wang X, Dai L. Mechanisms of isoniazid and rifampicin-induced liver injury and the effects of natural medicinal ingredients: A review. Front Pharmacol. 2022 Oct 10;13:1037814. doi: 10.3389/fphar.2022.1037814.
21. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O, Peter JU. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst Rev. 2022;7(7):CD012432. doi:10.1002/14651858.CD012432.pub3
22. Ahmet A, Mokashi A, Goldbloom EB, Huot C, Jurencak R, Krishnamoorthy P, et al. Adrenal suppression from glucocorticoids: preventing an iatrogenic cause of morbidity and mortality in children. BMJ Paediatr Open. 2019 Oct 23;3(1):e000569. doi: 10.1136/bmjpo-2019-000569.
23. Irfan N, Samuel E, Rafi Ranjha F, Waheed A, Abu Bakar M, Usman S, et al. Toxicity Profile of Procarbazine Lomustine and Vincristine Chemotherapy in Low-Grade Glioma - Retrospective Review. Cureus. 2020 Oct 20;12(10):e11070. doi: 10.7759/cureus.11070.
24. Cornett EM, Novitch M, Kaye AD, Kata V, Kaye AM. Medication-Induced Tardive Dyskinesia: A Review and Update. Ochsner J. 2017 Summer;17(2):162-174.

25. Güveli BT, Rosti RÖ, Güzeltaş A, Tuna EB, Ataklı D, Sencer S, et al. Teratogenicity of Antiepileptic Drugs. Clin Psychopharmacol Neurosci. 2017 Feb 28;15(1):19-27. doi: 10.9758/cpn.2017.15.1.19.

26. Buchanich JM, Newcomb CW, Washington TL, Foster CS, Sobrin L, Thorne JE, et al. Use of immunosuppression and subsequent cancer incidence: cohort study: BMJ Oncology 2023;2:e000037.

27. Maust DT, Petzold K, Strominger J, Kim HM, Bohnert ASB. Benzodiazepine Discontinuation and Mortality Among Patients Receiving Long-Term Benzodiazepine Therapy. JAMA Netw Open. 2023 Dec 1;6(12):e2348557. doi: 10.1001/jamanetworkopen.2023.48557.

28. Neumann A, Maura G, Weill A, Alla F, Danchin N. Clinical Events After Discontinuation of β-Blockers in Patients Without Heart Failure Optimally Treated After Acute Myocardial Infarction: A Cohort Study on the French Healthcare Databases. Circ Cardiovasc Qual Outcomes. 2018;11(4):e004356. doi:10.1161/CIRCOUTCOMES.117.004356.

29. Avery N, McNeilage AG, Stanaway F, Ashton-James CE, Blyth FM, Martin R, et al. Efficacy of interventions to reduce long term opioid treatment for chronic non-cancer pain: systematic review and meta-analysis. BMJ. 2022 Apr 4;377:e066375. doi: 10.1136/bmj-2021-066375.

30. Bauer PR, Ostermann M, Russell L, Robba C, David S, Ferreyro BL, et al. Plasma exchange in the intensive care unit: a narrative review. Intensive Care Med. 2022 Oct;48(10):1382-1396. doi: 10.1007/s00134-022-06793-z.

31. Cervantes CE, Bloch EM, Sperati CJ. Therapeutic Plasma Exchange: Core Curriculum 2023. Am J Kidney Dis. 2023 Apr;81(4):475-492. doi: 10.1053/j.ajkd.2022.10.017.

32. Tornio A, Filppula AM, Niemi M, Backman JT. Clinical Studies on Drug-Drug Interactions Involving Metabolism and Transport: Methodology, Pitfalls, and Interpretation. Clin Pharmacol Ther. 2019 Jun;105(6):1345-1361. doi: 10.1002/cpt.1435.

33. Malki MA, Pearson ER. Drug-drug-gene interactions and adverse drug reactions. Pharmacogenomics J. 2020 Jun;20(3):355-366. doi: 10.1038/s41397-019-0122-0.

34. Stielow M, Witczyńska A, Kubryń N, Fijałkowski Ł, Nowaczyk J, Nowaczyk A. The Bioavailability of Drugs-The Current State of Knowledge. Molecules. 2023 Dec 11;28(24):8038. doi: 10.3390/molecules28248038.

35. Al-Qassabi J, Tan SPF, Phonboon P, Galetin A, Rostami-Hodjegan A, Scotcher D. Facing the Facts of Altered Plasma Protein Binding: Do Current Models Correctly Predict Changes in Fraction Unbound in Special Populations? J Pharm Sci. 2024 Jun;113(6):1664-1673. doi: 10.1016/j.xphs.2024.02.024.

36. Vintila BI, Arseniu AM, Butuca A, Sava M, Bîrluțiu V, Rus LL, et al. Adverse Drug Reactions Relevant to Drug Resistance and Ineffectiveness Associated with Meropenem, Linezolid, and Colistin: An Analysis Based on Spontaneous Reports from the European Pharmacovigilance Database. Antibiotics (Basel). 2023 May 16;12(5):918. doi: 10.3390/antibiotics12050918.

37. Rahman S, Kesselheim AS, Hollis A. Persistence of resistance: a panel data analysis of the effect of antibiotic usage on the prevalence of resistance. J Antibiot (Tokyo). 2023 May;76(5):270-278. doi: 10.1038/s41429-023-00601-6.

38. Mahin J, Peddireddy M, Mangalapalli V, Padi SSV. Antibiotic prescribing practice in chronic kidney disease patients in a tertiary care teaching hospital: analysis based on 2019 WHO AWaRe Classification: Int J Life Sci Pharm Res. 2021;11(4):P49-P57. https://doi.org/10.22376/ijpbs/lpr.2021.11.4.P49-57

39. Calderón-Ospina C, Bustamante-Rojas C. The DoTS classification is a useful way to classify adverse drug reactions: a preliminary study in hospitalized patients. Int J Pharm Pract. 2010 Aug;18(4):230-5. doi: 10.1111/j.2042-7174.2010.00039.x.

40. Tian Y, Hua W, Wu Y, Zhang T, Wang W, Wu H, et al. Immune Response to Hepatitis B Virus Vaccine Among People Living With HIV: A Meta-Analysis. Front Immunol. 2021 Dec 22;12:745541. doi: 10.3389/fimmu.2021.745541.

41. Kostner L, Anzengruber F, Guillod C, Recher M, Schmid-Grendelmeier P, Navarini AA. Allergic Contact Dermatitis. Immunol Allergy Clin North Am. 2017;37(1):141-152. doi:10.1016/j.iac.2016.08.014

42. Ergen EN, Hughey LC. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. JAMA Dermatol. 2017;153(12):1344. doi:10.1001/jamadermatol.2017.3957

43. González-García R, Albanell-Fernández M, Aranda L, Gelis S, Bartra J, Soy Muner D, López-Cabezas C. Evaluation of desensitization protocols to betalactam antibiotics. J Clin Pharm Ther. 2022 May;47(5):592-599. doi: 10.1111/jcpt.13578.

44. Digiovanni-Kinsley S, Duke B, Giovane R, Paisley C. A Case of Digoxin Toxicity Due to Acute Renal Failure. Cureus. 2021 Aug 31;13(8):e17599. doi: 10.7759/cureus.17599.

45. Andrews P, Anseeuw K, Kotecha D, Lapostolle F, Thanacoody R. Diagnosis and practical management of digoxin toxicity: a narrative review and consensus. Eur J Emerg Med. 2023 Dec 1;30(6):395-401. doi: 10.1097/MEJ.0000000000001065.

46. Austin JP, Foster BA, Empey A. Replace Red Man Syndrome with Vancomycin Flushing Reaction. Hosp Pediatr. 2020 Jul;10(7):623-624. doi: 10.1542/hpeds.2020-0125.

47. Vítovec J, Spinar J. Heart failure and first dose hypotension after angiotensin converting enzyme inhibitors. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2004;148(2):113-118. doi:10.5507/bp.2004.020

48. Toprak K, Kaplangöray M, Memioglu T, İnanır M, Biçer A, Demirbağ R, Erdoğdu H. The Relationship Between Nitrate-Induced Headache and -Blood Viscosity: An Observational Prospective Study. J Cardiovasc Pharmacol. 2023 Aug 1;82(2):162-168. doi: 10.1097/FJC.0000000000001443.

49. Vayne C, Guéry EA, Rollin J, Baglo T, Petermann R, Gruel Y. Pathophysiology and Diagnosis of Drug-Induced Immune Thrombocytopenia. J Clin Med. 2020 Jul 13;9(7):2212. doi: 10.3390/jcm9072212.

50. Asim M, Ahmad F, Akhtar M. Florid Interstitial Hemorrhages: A Novel Feature of Amoxicillin-Clavulanate-Induced Acute Tubulointerstitial Nephritis. Am J Case Rep. 2021;22:e928989. doi:10.12659/AJCR.928989

51. Rutkowski K, Li PH, Wagner A. The Paradox of Antihistamine Hypersensitivity. J Allergy Clin Immunol Pract. 2018 Jan-Feb;6(1):258-259. doi: 10.1016/j.jaip.2017.10.035.

52. Balakirski G, Merk HF. Cutaneous allergic drug reactions: update on pathophysiology, diagnostic procedures and differential diagnosic. Cutan Ocul Toxicol. 2017;36(4):307-316. doi:10.1080/15569527.2017.1319379

53. Karachalios GN, Charalabopoulos A, Papalimneou V, et al. Withdrawal syndrome following cessation of antihypertensive drug therapy. Int J Clin Pract. 2005;59(5):562-570. doi:10.1111/j.1368-5031.2005.00520.x

54. Taguchi K, Bessho N, Hasegawa M, Narimatsu H, Matsumoto T, Kobayashi T. Co-treatment with clonidine and a GRK2 inhibitor prevented rebound hypertension and endothelial dysfunction after withdrawal in diabetes. Hypertens Res. 2018;41(4):263-274. doi:10.1038/s41440-018-0016-6

55. Wamakima BW, McKinney S, Bookman L, Gompers A, Hacker MR, Farid H. Postmenopausal Vaginal and Cervical Cancer Risk Related to In Utero Diethylstilbestrol Exposure. J Low Genit Tract Dis. 2023;27(1):35-39. doi:10.1097/LGT.0000000000000713

56. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015 Jun;105(2):140-56. doi: 10.1002/bdrc.21096.

57. Thomseth V, Cejvanovic V, Jimenez-Solem E, Petersen KM, Poulsen HE, Andersen JT. Exposure to topical chloramphenicol during pregnancy and the risk of congenital malformations: a Danish nationwide cohort study. Acta Ophthalmol. 2015 Nov;93(7):651-3. doi: 10.1111/aos.12737.

58. Hintze JP, Edinger JD. Hypnotic Discontinuation in Chronic Insomnia. Sleep Med Clin. 2020 Jun;15(2):147-154. doi: 10.1016/j.jsmc.2020.02.003.

59. Jovičić Burić D, Muslić L, Krašić S, Markelić M, Pejnović Franelić I, Musić Milanović S. Gender Differences in the Prediction of Alcohol Intoxication among Adolescents. Subst Use Misuse. 2021;56(7):1024-1034. doi: 10.1080/10826084.2021.1906278.

60. Nevin RL, Leoutsakos JM. Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event Reporting System Data. Drugs R D. 2017 Mar;17(1):199-210. doi: 10.1007/s40268-016-0167-3.

61. Yılmaz İ. Angiotensin-Converting Enzyme Inhibitors Induce Cough. Turk Thorac J. 2019 Jan 1;20(1):36-42. doi: 10.5152/TurkThoracJ.2018.18014.

62. He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. Curr Opin Rheumatol. 2018 Sep;30(5):490-497. doi: 10.1097/BOR.0000000000000522.

63. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. Curr Opin Neurol. 2019 Apr;32(2):246-252. doi: 10.1097/WCO.0000000000000659.

64. Jangid SD, Saoji V, Madke B, Bhatt DM. Drug-Induced Pseudoporphyria: A Case Report. Cureus. 2024 Apr 4;16(4):e57574. doi: 10.7759/cureus.57574.

65. Douville NJ, Kheterpal S, Engoren M, Mathis M, Mashour GA, Hornsby WE, et al. Genetic mutations associated with susceptibility to perioperative complications in a longitudinal biorepository with integrated genomic and electronic health records. Br J Anaesth. 2020 Dec;125(6):986-994. doi: 10.1016/j.bja.2020.08.009.

66. Gregory H, Weant KA. Pathophysiology and Treatment of Malignant Hyperthermia. Adv Emerg Nurs J. 2021;43(2):102-110. doi:10.1097/TME.0000000000000344

67. Arellano AL, Martin-Subero M, Monerris M, LLerena A, Farré M, Montané E. Multiple adverse drug reactions and genetic polymorphism testing: A case report with negative result. Medicine (Baltimore). 2017 Nov;96(45):e8505. doi: 10.1097/MD.0000000000008505.

68. Petric Z, Žuntar I, Putnik P, Bursać Kovačević D. Food-Drug Interactions with Fruit Juices. Foods. 2020;10(1):33. Published 2020 Dec 24. doi:10.3390/foods10010033

69. Łukawska E, Frankiewicz D, Izak M, Woźniak A, Dworacki G, Niemir ZI. Lithium toxicity and the kidney with special focus on nephrotic syndrome associated with the acute kidney injury: A case-based systematic analysis. J Appl Toxicol. 2021;41(12):1896-1909. doi:10.1002/jat.4167

70. Moon AM, Jiang Y, Rogal SS, Becker J, Barritt AS 4th. In inpatients with cirrhosis, opioid use is common and associated with length of stay and persistent use post-discharge. PLoS One. 2020 Feb 26;15(2):e0229497. doi: 10.1371/journal.pone.0229497.

71. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ. 2003;327(7425):1222-1225. doi:10.1136/bmj.327.7425.1222

72. Ilias I, Milionis C, Zoumakis E. An Overview of Glucocorticoid-Induced Osteoporosis. [Updated 2022 Mar 19]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278968/

73. Doña I, Guidolin L, Bogas G, Olivieri E, Labella M, Schiappoli M, et al. Resensitization in suspected penicillin allergy. Allergy. 2023 Jan;78(1):214-224. doi: 10.1111/all.15508.

74. Oscanoa TJ, Vidal X, Luque J, Julca DI, Romero-Ortuno R. Hepatotoxicity induced by isoniazid in patients with latent tuberculosis infection: a meta-analysis. Gastroenterol Hepatol Bed Bench. 2023;16(1):448-457. doi: 10.22037/ghfbb.v16i1.2685.

75. Murdaugh LB. Adverse Drug Reaction Reporting. Chapter 40; Competence Assessment Tools for Health-System Pharmacies. 545-556. Accessed on 24 June 2024. Available: https://www.ashp.org/-/media/store-files/p4023-sample-chapter-40.ashx

76. Cervantes-Arellano MJ, Castelán-Martínez OD, Marín-Campos Y, Chávez-Pacheco JL, Morales-Ríos O, Ubaldo-Reyes LM. Educational interventions in pharmacovigilance to improve the knowledge, attitude and the report of adverse drug reactions in healthcare professionals: Systematic Review and Meta-analysis. Daru. 2024 Jun;32(1):421-434. doi: 10.1007/s40199-024-00508-z.

77. Verman S, Anjankar A. A Narrative Review of Adverse Event Detection, Monitoring, and Prevention in Indian Hospitals. Cureus 14(9): e29162. doi:10.7759/cureus.29162

78. Ribeiro-Vaz I, Silva AM, Costa Santos C, Cruz-Correia R. How to promote adverse drug reaction reports using information systems - a systematic review and meta-analysis. BMC Med Inform Decis Mak. 2016 Mar 1;16:27. doi: 10.1186/s12911-016-0265-8.

79. Gonzalez-Gonzalez C, Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Strategies to improve adverse drug reaction reporting: a critical and systematic review. Drug Saf. 2013 May;36(5):317-28. doi: 10.1007/s40264-013-0058-2.

80. Kaufman G. Adverse drug reactions: classification, susceptibility and reporting. Nurs Stand. 2016;30(50):53-63. doi:10.7748/ns.2016.e10214

81. Lucas S, Ailani J, Smith TR, Abdrabboh A, Xue F, Navetta MS. Pharmacovigilance: reporting requirements throughout a product's lifecycle. Ther Adv Drug Saf. 2022;13:20420986221125006. doi:10.1177/20420986221125006

82. Raj N, Fernandes S, Charyulu NR, Dubey A, G S R, Hebbar S. Postmarket surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. Ther Adv Drug Saf. 2019;10:2042098619865413. doi:10.1177/2042098619865413

83. Laatikainen O, Sneck S, Turpeinen M. Medication-related adverse events in health care-what have we learned? A narrative overview of the current knowledge. Eur J Clin Pharmacol. 2022;78(2):159-170. doi:10.1007/s00228-021-03213-x

84. Venkatasubbaiah M, Dwarakanadha Reddy P, Satyanarayana SV. Analysis and reporting of adverse drug reactions at a tertiary care teaching hospital. Alexandria J Med. 2018;54(4),597-603. doi10.1.16/j.ajme.2018.10.005

85. Fossouo Tagne J, Yakob RA, Dang TH, Mcdonald R, Wickramasinghe N. Reporting, Monitoring, and Handling of Adverse Drug Reactions in Australia: Scoping Review. JMIR Public Health Surveill. 2023;9:e40080. Published 2023 Jan 16. doi:10.2196/40080

86. Khardali A. Exploring the knowledge, perception, and practice of community pharmacists in Saudi Arabia toward pharmacovigilance and adverse drug reaction reporting. A nationwide survey. Sci Rep. 2024 Feb 27;14(1):4819. doi: 10.1038/s41598-024-55664-8.

87. Salazar A, Amato MG, Shah SN, Khazen M, Aminmozaffari S, Klinger EV, Volk LA, Mirica M, Schiff GD. Pharmacists' role in detection and evaluation of adverse drug reactions: Developing

proactive systems for pharmacosurveillance. Am J Health Syst Pharm. 2023 Feb 15;80(4):207-214. doi: 10.1093/ajhp/zxac325.

88. Karuppannan M, Mohamad Rizal NAN, Wong KT, Mohd Ali S, Ting KN, Boardman H. Pharmacists' experiences on adverse drug reaction: 10 years later. Front Pharmacol. 2022 Sep 29;13:932942. doi: 10.3389/fphar.2022.932942.

89. Srisuriyachanchai W, Cox AR, Jarernsiripornkul N. Exploring Healthcare Professionals' Practices and Attitudes towards Monitoring and Reporting of Severe Adverse Drug Reactions. Healthcare (Basel). 2022 Jun 10;10(6):1077. doi: 10.3390/healthcare10061077.

90. Guidelines for Detecting & Reporting Adverse Drug Reactions. Individual Case Safety Reports For Healthcare Professionals. Accessed on 24 June 2024. Available: https://who-umc.org/media/1079/jordan.pdf

91. Kalaiselvan V, Thota P, Singh GN. Pharmacovigilance Programme of India: Recent developments and future perspectives. Indian J Pharmacol. 2016 Nov-Dec;48(6):624-628. doi: 10.4103/0253-7613.194855.

92. Tsuchiya M, Obara T, Miyazaki M, Noda A, Sakai T, Funakoshi R, Mano N. High-quality reports and their characteristics in the Japanese Adverse Drug Event Report database (JADER). J Pharm Pharm Sci. 2021;24:161-173.

93. Trenque A, Rabiaza A, Fedrizzi S, Chretien B, Sassier M, Morello R, et al. Evaluation of a simplified pharmacovigilance tool for general practitioners: 5 years of insight. Sci Rep. 2024 Jan 20;14(1):1766. doi: 10.1038/s41598-024-51753-w.

94. Mall SK, Dipa P, Goswami S, Singh P, Singh RP. Pharmacovigilance programme in India (PvPI): History, Current scenario, future aspects and role in COVID 19. Asian J Res in Pharm Sci. 2022; 12(3):205-9. doi: 10.52711/2231-5659.2022.00036

95. Sienkiewicz K, Burzyńska M, Rydlewska-Liszkowska I, Sienkiewicz J, Gaszyńska E. The Importance of Direct Patient Reporting of Adverse Drug Reactions in the Safety Monitoring Process. Int J Environ Res Public Health. 2021 Dec 31;19(1):413. doi: 10.3390/ijerph19010413.

96. Hasford J, Bruchmann F, Lutz M, Thürmann P, Schmiedl S. A patient-centred web-based adverse drug reaction reporting system identifies not yet labelled potential safety issues. Eur J Clin Pharmacol. 2021 Nov;77(11):1697-1704. doi: 10.1007/s00228-021-03134-9.

97. de Vries ST, Denig P, Andrić A, Dimov Di Giusti M, Ptaszynska-Neophytou A, Härmark L, Mol PGM; IMI Web-RADR Work Package 3b Consortium and SCOPE Joint Action Work Package 4. Motives to Report Adverse Drug Reactions to the National Agency: A Survey Study among Healthcare Professionals and Patients in Croatia, The Netherlands, and the UK. Drug Saf. 2021 Oct;44(10):1073-1083. doi: 10.1007/s40264-021-01098-4.

98. Cervantes-Arellano MJ, Castelán-Martínez OD, Marín-Campos Y, Chávez-Pacheco JL, Morales-Ríos O, Ubaldo-Reyes LM. Educational interventions in pharmacovigilance to improve the knowledge, attitude and the report of adverse drug reactions in healthcare professionals: Systematic Review and Meta-analysis. Daru. 2024 Jun;32(1):421-434. doi: 10.1007/s40199-024-00508-z.

99. Shafei L, Mekki L, Maklad E, et al. Factors that influence patient and public adverse drug reaction reporting: a systematic review using the theoretical domains framework. Int J Clin Pharm. 2023;45(4):801-813. doi:10.1007/s11096-023-01591-z

100. Rolfes L, van Hunsel F, van der Linden L, Taxis K, van Puijenbroek E. The Quality of Clinical Information in Adverse Drug Reaction Reports by Patients and Healthcare Professionals: A Retrospective Comparative Analysis. Drug Saf. 2017 Jul;40(7):607-614. doi: 10.1007/s40264-017-0530-5.

101. Bégaud B, Judith KJ. Assessing causality from case reports. In: Strom BL, Kimmel SE, Hennessy S, editors. Textbook of pharmacoepidemiology. 3. New York: Wiley; 2021. pp. 246–256.

102. Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et l. The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement. Drug Saf. 2024 Jun;47(6):575-584. doi: 10.1007/s40264-024-01421-9.

103. Smyth RL, Peak M, Turner MA, et al. ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods. Southampton (UK): NIHR Journals Library; 2014 Jun. (Programme Grants for Applied Research, No. 2.3.) Chapter 5, Causality assessment of adverse drug reactions. Available from: https://www.ncbi.nlm.nih.gov/books/NBK262740/

104. Pramod Kumar A, Bhoopathi D, Sunkara H, Chalasani SH. An overview of various scales used in causality assessment of adverse drug reactions. Int J Pharm Pharm Sci. 2020;12(5):1-5.

105. Pande S. Causality or Relatedness Assessment in Adverse Drug Reaction and Its Relevance in Dermatology. Indian J Dermatol. 2018 Jan-Feb;63(1):18-21. doi: 10.4103/ijd.IJD_579_17.

106. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31(1):21-37. doi: 10.2165/00002018-200831010-00003.

107. Kumaraswamy M, Mohan A, Chonari TA, Dahim M. Adverse Drug Reaction Tools Used in Causality Assessment. Indian J Pharmacy Practice. 2023;16(4):281-8.

108. Varallo FR, Planeta CS, Herdeiro MT, Mastroianni PC. Imputation of adverse drug reactions: Causality assessment in hospitals. PLoS One. 2017 Feb 6;12(2):e0171470. doi: 10.1371/journal.pone.0171470.

109. Aung AK, Walker S, Khu YL, Tang MJ, Lee JI, Graudins LV. Adverse drug reaction management in hospital settings: review on practice variations, quality indicators and education focus. Eur J Clin Pharmacol. 2022;78(5):781-791. doi:10.1007/s00228-022-03287-1

110. Pharmacovigilance Programme of India (PvPI) and Advantages of Enrolment as Adverse Drug Reaction Monitoring Centre (AMC) under PvPI. Accessed on 25 June 2024. Available: https://nabh.co/Announcement/Expansion%20of%20Pharmacovigilance%20Programme%20of%20India.pdf

111. Pabbathi N, Pasupulati H, Gaddam S, Padi SSV. The World of Vaccines: Phases of Clinical Trials and Current Status of COVID-19 Vaccines. Asian J Pharm Res Dev.2023;11(3):151–167. https://doi.org/10.22270/ajprd.v11i3.1273

112. van Staa TP, Pirmohamed M, Sharma A, Ashcroft DM, Buchan I. Adverse drug reactions and hospital admissions: Large case-control study of patients aged 65-100 years using linked English primary care and hospital data. Pharmacoepidemiol Drug Saf. 2024 Jan;33(1):e5681. doi: 10.1002/pds.5681.

113. Giardina C, Cutroneo PM, Mocciaro E, Russo GT, Mandraffino G, Basile G, et al. Adverse Drug Reactions in Hospitalized Patients: Results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study. Front Pharmacol. 2018 Apr 11;9:350. doi: 10.3389/fphar.2018.00350.

114. Sugioka M, Tachi T, Mizui T, Koyama A, Murayama A, Katsuno H, et al. Effects of the number of drugs used on the prevalence of adverse drug reactions in children. Sci Rep. 2020 Dec 7;10(1):21341. doi: 10.1038/s41598-020-78358-3.

115. Balon M, Tessier S, Damase-Michel C, Cottin J, Lambert A, Thompson MA, et al. Adverse drug reactions in pregnant women: Do they differ from those in non-pregnant women of childbearing age? Therapie. 2023 Mar-Apr;78(2):165-173. doi: 10.1016/j.therap.2022.11.005.

116. Gray SL, Perera S, Soverns T, Hanlon JT. Systematic Review and Meta-analysis of Interventions to Reduce Adverse Drug Reactions in Older Adults: An Update. Drugs Aging. 2023 Nov;40(11):965-979. doi: 10.1007/s40266-023-01064-y.

117. Peddireddy M, Mahin J, Uppu A, Padi SSV. Hospital Antibiotic Prescribing Pattern in General Surgery Specialty: Analysis Based on the WHO Access, Watch and Reserve (AWaRe) Classification. J Pharm Res Int. 2021;33(41B):7–19. doi: 10.9734/jpri/2021/v33i41B32339.

118. Pasupulati H, Avadhanula V, Mamilla A, Bamini M, Padi SSV. Antibiotic Prescribing Practices in Primary Care Settings Using 2019 WHO AWaRe Framework. J Pharm Res Int. 2021;33(37A):58–68. doi: 10.9734/jpri/2021/v33i37A31980.

119. Komagamine J. Prevalence of urgent hospitalizations caused by adverse drug reactions: a cross-sectional study. Sci Rep. 2024 Mar 13;14(1):6058. doi: 10.1038/s41598-024-56855-z.

120. Mejía G, Saiz-Rodríguez M, Gómez de Olea B, Ochoa D, Abad-Santos F. Urgent Hospital Admissions Caused by Adverse Drug Reactions and Medication Errors-A Population-Based Study in Spain. Front Pharmacol. 2020 May 21;11:734. doi: 10.3389/fphar.2020.00734.

121. Prasad N, Lau ECY, Wojt I, Penm J, Dai Z, Tan ECK. Prevalence of and Risk Factors for Drug-Related Readmissions in Older Adults: A Systematic Review and Meta-Analysis. Drugs Aging. 2024 Jan;41(1):1-11. doi: 10.1007/s40266-023-01076-8.

122. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt PMLA, Janssen MJA, Karapinar-Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am Geriatr Soc. 2018 Mar;66(3):602-608. doi: 10.1111/jgs.15244.

123. Schmid O, Bereznicki B, Peterson GM, Stankovich J, Bereznicki L. Persistence of Adverse Drug Reaction-Related Hospitalization Risk Following Discharge. Int J Environ Res Public Health. 2022 May 4;19(9):5585. doi: 10.3390/ijerph19095585.

124. Marra AR, Perencevich EN, Nelson RE, Samore M, Khader K, Chiang HY, et al. Incidence and Outcomes Associated With Clostridium difficile Infections: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Jan 3;3(1):e1917597. doi: 10.1001/jamanetworkopen.2019.17597.

125. Therapy Brands. Preventing Adverse Drug Reactions During Healthcare. Accessed on 26 June 2024. Available: https://therapybrands.com/blog/preventing-adverse-drug-reactions-during-healthcare/

126. Khalil H, Bell B, Chambers H, Sheikh A, Avery AJ. Professional, structural and organisational interventions in primary care for reducing medication errors. Cochrane Database Syst Rev. 2017 Oct 4;10(10):CD003942. doi: 10.1002/14651858.CD003942.pub3.

127. Jošt M, Kerec Kos M, Kos M, Knez L. Effectiveness of pharmacist-led medication reconciliation on medication errors at hospital discharge and healthcare utilization in the next 30 days: a pragmatic clinical trial. Front Pharmacol. 2024 Mar 28;15:1377781. doi: 10.3389/fphar.2024.1377781.

128. Nicholls J, MacKenzie C, Braund R. Preventing drug-related adverse events following hospital discharge: the role of the pharmacist. Integr Pharm Res Pract. 2017 Feb 13;6:61-69. doi: 10.2147/IPRP.S104639.

129. Cousins J, Parameswaran Nair N, Curtain C, Bereznicki B, Wilson K, Adamczewski B, et al. Preventing Adverse Drug Reactions After Hospital Discharge (PADR-AD): Protocol for a randomised-controlled trial in older people. Res Social Adm Pharm. 2022 Aug;18(8):3284-3289. doi: 10.1016/j.sapharm.2021.09.007.

130. Nguyen KA, Militello LG, Ifeachor A, Arthur KJ, Glassman PA, Zillich AJ, et al. Strategies prescribers and pharmacists use to identify and mitigate adverse drug reactions in inpatient and outpatient care: a cognitive task analysis at a US Veterans Affairs Medical Center. BMJ Open. 2022 Feb 21;12(2):e052401. doi: 10.1136/bmjopen-2021-052401.

131. Scott EN, Hasbullah JS, Carleton BC, Ross CJD. Prevention of adverse drug effects: a pharmacogenomic approach. Curr Opin Pediatr. 2020 Oct;32(5):646-653. doi: 10.1097/MOP.0000000000000935.

132. Zhao H, Ni P, Zhao Q, Liang X, Ai D, Erhardt S, Wang J, Li Y, Wang J. Identifying the serious clinical outcomes of adverse reactions to drugs by a multi-task deep learning framework. Commun Biol. 2023 Aug 24;6(1):870. doi: 10.1038/s42003-023-05243-w.

133. Gaddam S, Pasupulati H, Padi SSV. Vaccines Versus Covid-19 Vaccines: Maneuver timeline of development and trial designs: Development of Vaccines and COVID-19 Vaccines. World J Current Med Pharm Res. 2023;5(3):51-61. doi:10.37022/wjcmpr.v5i3.265

134. Delgado-Pérez G, Dávila-Espinoza C, Beltran-Noblega C. Impact of the Role of the Clinical Pharmacist on the Underreporting of Adverse Drug Reactions at a Peruvian hospital. Hosp Pharm. 2023 Jun;58(3):295-303. doi: 10.1177/00185787221138006.

135. Stashluk S, Ramos M, Carettini T, Cutrell JB, Mathew S, Monogue M, et al. Bridging the gap: opportunities for transitions of care pharmacist review of outpatient parenteral antimicrobial therapy prescriptions prior to hospital discharge. Antimicrob Steward Healthc Epidemiol. 2024 Apr 18;4(1):e50. doi: 10.1017/ash.2024.52.

136. Warunek LN, Gruver B, Bartko L, Blair J. Assessing intradisciplinary pharmacy communication related to transitions of care. Explor Res Clin Soc Pharm. 2024 Apr 4;14:100438. doi: 10.1016/j.rcsop.2024.100438.