ISSN: 2767-8245

Available online on http://www.ijdcs.com/

International Journal of Dental and Clinical Studies 2026; 7(1) 7-13

Adverse Drug Reactions: Recognition, Causality Assessment, Reporting and Prevention – A Narrative Review

Anita Gurjar[1], Mehul Kumar Kumawat[2], Sudhakar Tyagi[3]

[1,2]Scholar Sri Balaji College of Pharmacy, Jaipur, Rajasthan, India
[3]Assistant Professor, Sri Balaji College of Pharmacy, Jaipur, Rajasthan, India

Corresponding author: Anita Gurjar
Conflict of interest: No conflict of interest

Abstract:
Adverse drug reactions (ADRs) are unintended and harmful responses associated with medicines used at normally recommended doses and remain an important challenge to safe and rational pharmacotherapy. Although pre-marketing clinical trials provide essential information on efficacy and common safety outcomes, uncommon, delayed and population-specific reactions may become apparent only after wider clinical use. Effective pharmacovigilance therefore requires continuous detection, assessment, documentation, reporting and prevention of medicine-related harm. This narrative review summarizes the concept and classification of ADRs, epidemiology and clinical burden, patient- and medicine-related risk factors, mechanisms and manifestations, causality assessment, severity, seriousness and preventability, pharmacovigilance systems, ADR detection and reporting, the Pharmacovigilance Programme of India (PvPI), management, prevention and risk minimization, the role of pharmacists and patient education. The traditional Type A–F classification remains useful for organizing clinical reasoning, while structured approaches such as the Naranjo algorithm support consistent causality assessment. Reporting does not require absolute certainty; a well-documented suspicion may contribute to signal detection when reports accumulate. Modern pharmacovigilance increasingly combines spontaneous reporting with active surveillance, electronic health records, targeted monitoring, and data mining and risk-based approaches. Pharmacists have an important role in medication review, recognition, counselling, documentation and reporting. Strengthening reporting culture, standardized documentation, interprofessional communication and patient participation can reduce preventable harm and improve medicine safety.
Keywords: Adverse drug reaction; Pharmacovigilance; Causality assessment; Naranjo algorithm; ADR reporting; Patient safety; Pharmacist; PvPI.

Introduction

Medicines are indispensable to modern healthcare and are used for prevention, diagnosis, treatment and maintenance of health. Their benefits, however, are accompanied by the possibility of unwanted effects. ADRs may reduce treatment adherence, prolong hospitalization, increase healthcare utilization and, in severe cases, cause disability or death.

Importantly, the occurrence of an ADR does not necessarily imply a medication error; a reaction may arise despite appropriate prescribing and administration. Recognition of ADRs is therefore an essential component of pharmaceutical care.

Assessment begins with a clear history of current and recently used medicines, including prescription medicines, over-the-counter products, herbal preparations, supplements and intermittently used therapies. The timing of exposure and onset of symptoms is particularly important. Dose changes, treatment duration, concomitant medicines, underlying diseases and patient-specific risk factors should also be reviewed. Pharmacovigilance extends this individual clinical activity into a systematic public-health process. It is concerned with the detection, assessment, understanding and prevention of adverse effects and other medicine-related problems. Its objective is not merely to count reactions, but to generate evidence that can improve the benefit–risk balance of medicines and support safer use. Clinical trials cannot identify every possible safety problem because their populations, sample sizes and observation periods are limited. Rare reactions, delayed effects, interactions and reactions in patients with multiple diseases may emerge only after broader exposure. Continuous post-marketing surveillance therefore complements pre-marketing evaluation and supports clinical and regulatory decision-making [1–3].

Concept and Definition of Adverse Drug Reactions

An ADR is generally understood as a harmful and unintended response to a medicinal product occurring at doses normally used in humans for prophylaxis, diagnosis or therapy. It should be distinguished from the broader term adverse event, which describes any untoward medical occurrence during treatment without requiring a causal relationship with the medicine. This distinction is important when interpreting safety information.

ADRs should also be differentiated from medication errors. Errors may occur during prescribing, transcribing, dispensing, administration or monitoring and can result in preventable harm. An ADR may instead occur when a medicine has been used correctly. Nevertheless, medication errors, non-adherence, drug interactions and product-quality problems can contribute to medicine-related harm and may need to be captured within broader patient-safety and pharmacovigilance systems [1,4]. Accurate terminology improves communication. Documentation should describe the clinical event, suspected medicine, relevant timing and supporting evidence without claiming certainty that the available information cannot establish.

Classification of Adverse Drug Reactions

The traditional Type A–F classification provides a practical framework for teaching and initial clinical reasoning. Type A (augmented) reactions are related to the known pharmacological action of a medicine and are often dose-dependent.

Examples include hypoglycaemia associated with glucose-lowering therapy and excessive anticoagulant effect. They are generally predictable and may be reduced by dose adjustment or monitoring.

Type B (bizarre) reactions are less predictable and are not usually explained by the usual pharmacological action. Hypersensitivity and idiosyncratic reactions are common examples. Type C (chronic) reactions are associated with long-term treatment or cumulative exposure. Type D (delayed) reactions become apparent after a time interval and may sometimes be recognized after treatment has ended.

Type E (end-of-use) reactions occur after withdrawal and may represent rebound or withdrawal phenomena. Type F (failure of therapy) describes unexpected failure to produce the desired therapeutic effect; possible contributors include drug interactions, non-adherence, incorrect dose, and resistance or absorption problems.

Table 1:

Type	Characteristic	Typical approach
A – Augmented	Predictable; dose-related	Dose adjustment and monitoring
B – Bizarre	Unpredictable; hypersensitivity/idiosyncratic	Recognition and avoidance
C – Chronic	Cumulative/long-term exposure	Long-term monitoring
D – Delayed	Appears after time	Long-term surveillance
E – End-of-use	Withdrawal/rebound	Planned tapering where appropriate
F – Failure	Unexpected lack of efficacy	Check adherence, interactions and dose

Classification is not a substitute for clinical judgment. A patient can have more than one contributing factor, and clinical importance depends on severity, seriousness, preventability and consequences. The A–F system is most useful when it guides the questions asked during assessment and helps organize the evidence collected.

Epidemiology and Clinical Burden

The frequency of ADRs varies among populations, medicines, study designs and definitions. Hospitalized patients, older adults, individuals receiving multiple medicines and patients with impaired renal or hepatic function often require particular attention.

Differences in prescribing practices, reporting culture and surveillance methods also influence observed rates. Clinical trials generally detect common adverse effects under controlled conditions, but their inclusion criteria may exclude frail patients, patients with multiple diseases, pregnant patients and those receiving complex medication regimens. Rare reactions may require exposure of many thousands of people before becoming apparent. Post-marketing surveillance is therefore essential for detecting uncommon or unexpected signals. The burden of ADRs extends beyond the immediate clinical event. A reaction may lead to treatment interruption, additional investigations, emergency care, hospitalization, loss of productivity and increased costs.

Fear of adverse effects can also affect adherence, while under-recognition may result in unnecessary continuation or repeated exposure to a causative

medicine. Pharmacovigilance converts individual observations into collective learning: a single report may not establish causality, but clusters of similar reports can generate signals requiring investigation [1,5].

Risk Factors for Adverse Drug Reactions

ADR risk is influenced by patient-related, medicine-related, treatment-related and system-related factors. Age is important because pharmacokinetic and pharmacodynamic characteristics change throughout life. Older adults may have reduced renal or hepatic function, altered body composition and polypharmacy. Children require age- and weight-appropriate dosing and may have developmental differences in drug disposition. Renal or hepatic impairment can increase exposure to medicines dependent on these organs for elimination or metabolism.

Pregnancy and lactation require specialized consideration because both the mother and developing infant may be affected. Previous drug allergy or suspected hypersensitivity is an important warning factor and should be documented clearly. Medicine-related factors include high doses, narrow therapeutic index medicines, prolonged treatment, multiple concurrent therapies and medicines with known interaction potential.

Polypharmacy increases the number of possible drug–drug and drug–disease interactions and makes medication reconciliation more difficult. System factors include incomplete medication histories, ambiguous prescriptions, look-alike or sound-alike names, poor communication during transitions of care and inadequate counselling.

Table 2:

Risk category	Examples
Patient-related	Age extremes, renal/hepatic impairment, pregnancy, previous allergy
Medicine-related	High dose, narrow therapeutic index, polypharmacy, interactions
Treatment-related	Long duration, dose changes, complex regimens
System-related	Incomplete history, poor communication, confusing names

Mechanisms and Clinical Manifestations

ADRs may arise through predictable pharmacological effects, immune-mediated mechanisms, idiosyncratic responses, interactions or changes in drug exposure. Predictable reactions are often related to the intensity of the medicine's normal action, whereas unpredictable reactions may depend on host susceptibility or immunological mechanisms.

Clinical manifestations can involve virtually any organ system. Common symptoms include nausea, vomiting, abdominal discomfort, diarrhoea, constipation, dizziness, headache, drowsiness and skin rash. More serious presentations may include severe hypersensitivity, bronchospasm, hypotension, arrhythmia, major bleeding or organ injury.

Cutaneous reactions range from mild itching or maculopapular eruptions to severe reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Rapid recognition is important when mucosal involvement, blistering, skin detachment, systemic symptoms or rapid progression are present. Laboratory abnormalities such as elevated liver enzymes, changes in serum creatinine, electrolyte disturbances, cytopenias and abnormal coagulation parameters may provide additional evidence, but should be interpreted with baseline status, concurrent disease and other medicines in mind.

Causality Assessment

Causality assessment asks whether available evidence supports a relationship between a medicine and an observed event. The first step is to establish the temporal relationship: when the medicine was started, when the event began, and whether exposure or a dose change preceded the reaction. Alternative causes, concomitant medicines and underlying disease must then be considered. Dechallenge refers to observation of the clinical course after withdrawal or reduction of the suspected medicine. Improvement after withdrawal can strengthen the evidence in appropriate circumstances, although spontaneous recovery and other interventions can produce similar changes. Rechallenge may provide additional information when a reaction recurs after re-exposure, but deliberate rechallenge is generally inappropriate when the original reaction was severe or potentially life-threatening.

The Naranjo algorithm is a structured tool that assigns points to questions concerning temporal sequence, alternative causes, dechallenge, rechallenge, dose-response and previous reports. It can improve consistency, but its score should not be interpreted as absolute proof. Clinical judgment remains necessary because real-world cases may

contain incomplete information or multiple plausible explanations [6]. Causality assessment should never delay treatment of a serious reaction; stabilization takes priority while relevant information is documented as soon as practical.

Severity, Seriousness and Preventability

Severity and seriousness are related but distinct concepts. Severity describes the intensity of a reaction, such as mild, moderate or severe symptoms. Seriousness refers to outcomes such as death, life-threatening illness, hospitalization or prolongation of hospitalization, persistent or significant disability, or congenital anomaly. Preventability is another important dimension. Some reactions are difficult to predict and may occur despite appropriate use. Others may be associated with avoidable factors such as incorrect dose, drug interaction, duplication, inadequate monitoring or incomplete medication history. A complete ADR assessment should record the clinical outcome, interventions required, treatment changes, hospitalization status and suspected preventable contributors. Identifying preventability helps healthcare organizations move from reporting toward improvement.

Pharmacovigilance: Principles and Systems

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or other medicine-related problems. It operates across the medicine life cycle, from development through post-marketing use. It is multidisciplinary and supports safe, rational and effective use of medical products [1,4].

Spontaneous reporting remains a major source of post-marketing safety information. Healthcare professionals and, in many systems, patients can report suspected reactions even when causality is uncertain. Other methods include active surveillance, cohort studies, case-control studies, registries, targeted monitoring and electronic health-record analysis.

The WHO Programme for International Drug Monitoring was established in 1968 following global lessons from the thalidomide tragedy. The international network enables participating countries to contribute safety information and supports global signal detection. The Uppsala Monitoring Centre maintains the WHO global database VigiBase and provides technical support to the international pharmacovigilance network [5]. Contemporary pharmacovigilance increasingly emphasizes adaptive, coordinated and risk-based approaches, including integration with regulatory and health-system functions [7].

ADR Detection and Reporting

Detection begins with awareness. Healthcare professionals should consider an ADR whenever a new or worsening symptom, sign or laboratory abnormality appears during medicine exposure, particularly when the timing is plausible. A complete medication history should include prescription medicines, non-prescription products, herbal medicines, supplements and recent vaccinations where relevant.

A useful report should contain sufficient information to allow the event to be understood and followed up.

Important elements include patient information as permitted by the reporting system, suspected medicine and dose, indication, description of the reaction, dates of exposure and onset, outcome, concomitant medicines, relevant medical history and reporter details. Reports should describe the event without overstating causality. Follow-up information can strengthen a report by documenting recovery, stabilization, treatment provided and subsequent changes to therapy.

Under-reporting remains a practical challenge because of uncertainty, lack of time, limited awareness, fear of blame and difficulty accessing reporting systems. Education, simple reporting procedures, feedback to reporters and a non-punitive safety culture can improve participation.

Pharmacovigilance in India and PvPI

India has developed a national pharmacovigilance framework through the Pharmacovigilance Programme of India (PvPI), coordinated through the Indian Pharmacopoeia Commission. The programme aims to strengthen patient safety by collecting and evaluating suspected ADR reports from across the country and contributing to regulatory decision-making.

The Indian system includes ADR Monitoring Centres and mechanisms for reporting suspected reactions. India also contributes safety information to the WHO Programme for International Drug Monitoring. In 2017, the National Coordination Centre–PvPI at the Indian Pharmacopoeia Commission was designated as a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services [2,5].

The quality of reporting is critical because incomplete information limits the ability to assess signals. Continued reporting from hospitals, community settings and other healthcare environments can improve the representativeness of safety data and help identify medicine-related risks relevant to Indian patients [2,8].

Management of Adverse Drug Reactions

Management depends on the nature and seriousness of the reaction. The first priority is patient stabilization and appropriate clinical care. Depending on the situation, the suspected medicine may need to be stopped, withheld, dose-reduced or replaced after clinical evaluation. Severe hypersensitivity, significant bleeding, marked hypotension, respiratory compromise and other serious presentations require urgent treatment.

For predictable dose-related reactions, prevention and management may involve dose adjustment, therapeutic drug monitoring, renal or hepatic dose modification or closer observation. When interactions are suspected, the complete medication regimen should be reviewed rather than focusing only on one medicine. Allergy-like reactions require careful documentation of the suspected medicine and the nature of the reaction. Patients with serious hypersensitivity should receive clear instructions about future exposure, and the suspected allergy or ADR should be recorded in an accessible medication record. After acute management, follow-up is important. Clinical outcome, treatment changes and relevant laboratory results should be documented, and appropriate cases should be reported to pharmacovigilance systems.

Prevention and Risk Minimization

Preventing ADRs requires identification of high-risk patients and high-risk medicines before harm occurs. Medication reconciliation should be performed at transitions of care and whenever major changes are made. Prescribers and pharmacists should review allergies, duplicate therapy, potential interactions, dose appropriateness and monitoring requirements.

Patient counselling is a key preventive intervention. Patients should understand the purpose of each medicine, how and when to take it, important warning signs and when to seek medical help. They should be encouraged to disclose all medicines and supplements and to report previous suspected reactions.

Healthcare systems can reduce risk through standardized prescribing, electronic alerts, clinical protocols, therapeutic drug monitoring, clear labelling and structured handover. Safety interventions should be proportional to risk and should avoid alert fatigue. Organizations should review recurring ADRs, identify system weaknesses and implement corrective actions. A reporting culture should emphasize learning and patient safety rather than blame while maintaining professional accountability.

Role of the Pharmacist

Pharmacists are strategically positioned to support ADR prevention, detection, documentation and reporting. During dispensing and medication review, they can identify duplicate therapy, contraindications, interaction risks, inappropriate doses and medicines requiring closer monitoring.

Counselling creates an opportunity to explain expected effects and warning signs. Patients may disclose symptoms to pharmacists that they have not yet discussed with prescribers. Pharmacists can assess medication history, communicate concerns to the healthcare team and facilitate appropriate action.

Pharmacists also contribute to pharmacovigilance programmes, antimicrobial stewardship, medication reconciliation, safety audits and maintenance of allergy and ADR records. In hospital settings, participation in multidisciplinary rounds may improve early recognition of medicine-related problems. Professional education should include practical skills in ADR recognition, causality assessment, reporting procedures and patient communication.

Patient Education and Communication

Patients are active participants in medicine safety. Effective counselling should be understandable, individualized and focused on the medicine's purpose, correct administration, expected effects and important warning signs. Patients should be advised not to share medicines or change doses without appropriate medical advice.

An updated medicine list can reduce duplication and interaction risks, especially when a patient consults multiple healthcare professionals. Patients should be encouraged to report previous suspected allergies or ADRs and to mention over-the-counter medicines, supplements and herbal products. Communication should be particularly clear during transitions between hospital, outpatient and community care because incomplete transfer of medication information can lead to accidental re-exposure or omission of necessary therapy.

Illustrative Case Examples

Case 1 – Hypoglycaemia: A patient receiving glucose-lowering therapy develops sweating, tremor, confusion and a low blood glucose measurement. The presentation is consistent with a predictable pharmacological effect. Immediate clinical management is required, followed by review of dose, meal pattern, adherence and other medicines.

Case 2 – Drug-induced rash: A patient develops a generalized rash shortly after initiation of a new medicine. Medicine history, timing, severity, alternative causes and associated symptoms should

be assessed. Mucosal involvement, blistering, systemic symptoms or rapid progression would increase concern for a severe cutaneous reaction and require urgent medical evaluation.

Case 3 – Anticoagulant-associated bleeding: A patient receiving an anticoagulant presents with unexplained bleeding. The suspected medicine, dose, adherence, interacting medicines and relevant laboratory parameters should be reviewed promptly. Significant bleeding requires urgent clinical management. These examples demonstrate a common assessment framework: identify exposure, establish timing, evaluate severity and seriousness, consider alternative causes, manage the patient, document the outcome and report when appropriate.

Emerging Approaches in ADR Detection

Pharmacovigilance is increasingly supported by digital information sources. Electronic health records can facilitate targeted identification of laboratory abnormalities, clinical diagnoses, medication changes and outcomes. Automated signal detection can help prioritize large volumes of safety information for expert review.

Data-mining methods can identify disproportional reporting patterns within spontaneous-report databases. Such signals do not by themselves establish causality; they identify patterns requiring clinical and epidemiological evaluation.

Machine learning and natural-language processing are also being explored for extraction of adverse-event information from clinical narratives and other unstructured data. These technologies may reduce manual workload, but performance depends on data quality, validation, transparency and human oversight.

Risk-based and adaptive pharmacovigilance approaches are increasingly emphasized. Future systems are likely to combine conventional reporting with electronic records, targeted surveillance and analytical tools while maintaining standards for data quality, privacy and clinical interpretation [7].

Discussion: ADRs remain a continuing challenge because medicine safety is dynamic. The risk profile of a medicine can change as exposure increases, new populations receive treatment and new combinations of medicines are introduced. No single surveillance method can identify every possible safety problem. The reviewed evidence supports a layered approach. At the patient level, careful prescribing, medication reconciliation, monitoring and counselling reduce avoidable harm. At the healthcare-system level, standardized documentation, accessible reporting pathways and multidisciplinary communication improve detection. At national and international levels, aggregated reports and analytical systems support signal detection and regulatory action. Under-reporting remains a major limitation of spontaneous reporting. Improving the quality and accessibility of reporting may be more useful than simply increasing the number of reports. Reports should contain clinically meaningful information and be followed up when additional information becomes available. Pharmacists can bridge patients, prescribers and pharmacovigilance systems because their frequent contact with medicines and patients provides opportunities for early recognition.

Conclusion

Adverse drug reactions are important medicine-safety events that range from mild, predictable effects to severe and life-threatening reactions. Their recognition requires attention to medicine exposure, timing, dose, clinical presentation, alternative explanations and patient-specific risk factors. Causality assessment helps organize evidence but should always be interpreted alongside clinical judgment. Pharmacovigilance provides the framework for converting individual safety observations into broader learning. In India, the Pharmacovigilance Programme of India provides an important national mechanism for ADR surveillance and contributes to the international pharmacovigilance network. Prevention is a shared responsibility involving rational prescribing, medication reconciliation, interaction review, monitoring, counselling, documentation and timely reporting. Pharmacists have a particularly important role in maintaining this continuous medicine-safety process.

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