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ADVERSE DRUG REACTIONS

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Abstract: An adverse drug reaction (ADR) is a harmful and unforeseen response to a medication. ADRs drive up healthcare expenses and are a major contributor to morbidity and mortality. Adverse drug reactions (ADRs) continue to be a prevalent and serious issue in healthcare. Given the escalating complexity of treatments, the ageing population, and the rise in multimorbidity, adverse drug reactions (ADRs) continue to remain a challenge in contemporary healthcare. A suspected adverse drug reaction can be linked to a specific time, sickness pattern, investigational findings, and re-exposure. If at all possible, management include drug withdrawal as well as targeted therapy for any side effects. It is important to report suspected adverse drug reactions. In addition to examining issues related to their prevention, diagnosis, reporting, and management in current clinical practice, this article summarizes some of the most important information about ADRs.

Keywords: Adverse drug reactions , clinical pharmacology , drug-related side effects and adverse reactions , pharmacovigilance , adverse drug reaction reporting systems.

INTRODUCTION:

According to the definition of an adverse drug reaction (ADR), it is "an intervention associated to the use of a medical product that results in a significantly detrimental or unpleasant reaction; unfavorable effects typically indicate the likelihood of risk from subsequent administration and call for prevention, targeted therapy, a change in the dosing schedule, or the discontinuation of the medication."[1]

In addition to the approved use of a pharmaceutical product in typical doses, the term has expanded since 2012 to encompass reactions resulting from error, misuse, or abuse as well as suspected reactions to drugs that are not licensed or being used as off-label.[2] In clinical practice, this change shouldn't have an impact on how we manage ADRs, even though it may change how manufacturers and drug regulators record and monitor their products. ADRs are a prevalent manifestation in clinical practice, especially as a cause of unexpected hospital stays. Important research conducted in the USA and the UK in the late 20th and early 21st centuries showed that ADRs develop during hospital admission and appear after discharge.[3-6]

While research indicates that between 5% and 10% of patients may experience an ADR at admission, during hospitalization, or at discharge, despite numerous prevention measures, the incidence of ADRs has remained largely stable over time. The approach employed to identify such events is invariably correlated with the event frequency, and the majority of ADRs do not result in significant systemic signs. Nevertheless, given the related morbidity and mortality, the potential financial burden, and the potential impact on the prescriber-patient relationship, it is important to carefully examine the frequency of potential damage.

Antiplatelet, anticoagulant, cytotoxic, immunosuppressant, diuretic, antidiabetic, and antibiotic medications have all been specifically linked to ADR-related hospital admissions. When fatal ADRs do occur, hemorrhage is frequently to blame, with an antithrombotic/anticoagulant co-administered with a non-steroidal anti-inflammatory medicine being the most frequently suspected cause (NSAID).[7]

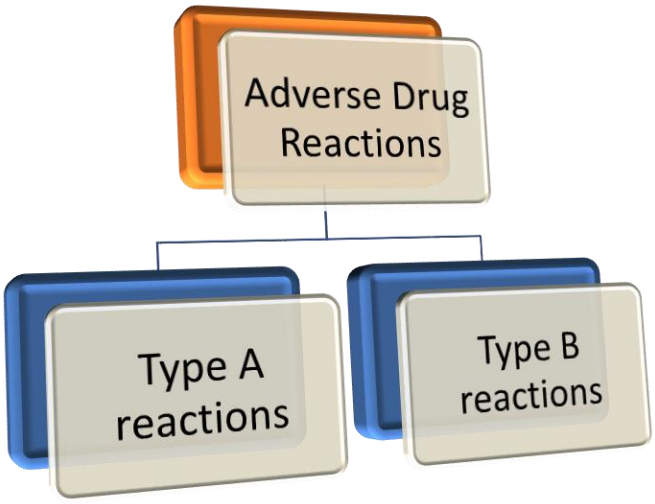

Fig 1: Classification of Adverse Drug Reactions

CLASSIFICATION OF ADVERSE DRUG REACTIONS:

ADRs have traditionally been divided into two categories:

1 - Type A reactions, which are 'dose-dependent' and predicable based on the drug's pharmacology, are also known as enhanced reactions.

2 - Type B reactions, often known as weird reactions, are unpredictable and idiosyncratic based on pharmacology.[8]

IMPORTANT POINTS:

- Unplanned hospital hospitalizations account for a sizeable share of adverse drug reactions (ADRs), unplanned, undesirable events that are linked to the use of medications. ADRs also happen during these admissions.
- A thorough medication history can help a prescriber comprehend the patient's prior drug treatment experiences, particularly in recognising prior adverse drug reactions (ADRs) that might prevent future exposure to the drug.
- Avoiding treatment in cohorts of patients who are more susceptible to adverse effects or administering treatment according to a therapeutic plan that lowers the likelihood of an adverse effect (e.g., co-administration of other medications, monitoring blood test results) are the two main ways to prevent ADRs.
- ADRs are grossly underreported generally across healthcare settings and sectors, despite spontaneous reporting (using the UK's Yellow Card Scheme) based on suspicion of an ADR being present. It is advisable to submit a report if unsure.

Although frequently cited, this fundamental classification does not apply to all ADRs, such as those with withdrawal reactions (such as rebound hypertension with the cessation of centrally acting antihypertensives) or long-term adverse effects associated with drug exposure (such as osteoporosis with long-term corticosteroid treatment). The "DoTS" classification system, which classifies reactions based on the drug dose, the time course of the reaction, and any pertinent susceptibility variables (such as genetic, pathological, and other biological characteristics)[9], is an alternative and perhaps more thorough system. DoTS has the advantage of being beneficial to take into account the diagnosis and prevention of ADRs in practise in addition to classifying reactions.

PREVENTING ADVERSE DRUG REACTIONS:

While certain adverse drug reactions (ADRs) are unanticipated, such anaphylaxis in a patient after a single uneventful exposure to an antibiotic containing penicillin, many may be avoided with enough planning and monitoring. When a drug treatment plan is preventable (or avoidable), it usually means that it does not follow the most recent evidence-based guidelines or is overly optimistic given the current situation.[10]

Between one-third and fifty percent of ADRs are (at least possibly) avoidable, according to epidemiological research, even though avoidability is far simpler to identify after the fact. However, one of the most effective ways to lower the risk of patient damage is by actions that lower the likelihood that an ADR will occur.

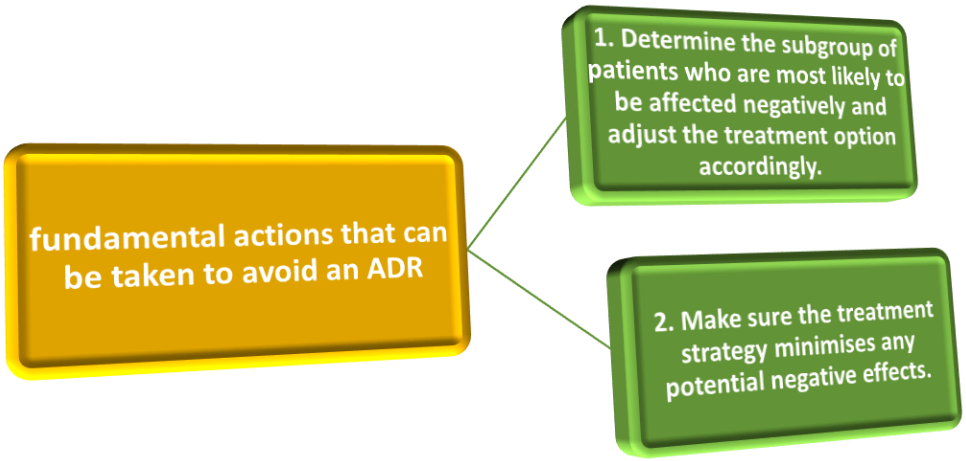

Fig 2: fundamental actions that can be taken to avoid an ADR

There are two fundamental actions that can be taken to avoid an ADR:

1. Determine the subgroup of patients who are most likely to be affected negatively and adjust the treatment option accordingly.

2. Make sure the treatment strategy minimises any potential negative effects.

IDENTIFY SUSCEPTIBILITY:

Your prescribing choice can be informed by patient susceptibilities, which lowers the likelihood of an adverse drug reaction. The medication history of a patient will reveal any prior ADRs and hence bar re-exposure to the medicine. In other situations, susceptibility variables including age, gender, pregnancy status, and ethnicity can aid in predicting the likelihood that an ADR would develop. For instance, the risk of ACE drug-induced angioedema has led the National Institute for Health and Care Excellence to advise against prescribing an ACE inhibitor for hypertension in patients of African or Caribbean heritage.

Instead, they should be given an angiotensin-II receptor blocker. Pharmacogenetics is beginning to produce more individualised treatment options by identifying patients who are more likely to experience a certain ADR (Table 1).

Clinical decision support tools that are available at the point of care can alert medical professionals to any patient-specific treatment precautions or demands for additional monitoring to lower the risk of damage. Although a thorough discussion is outside the scope of this work, practitioners should not rely on decision support systems since they can range greatly in their information-delivery capabilities, from the absence of pertinent alerts to information overload that causes alert fatigue.

TREATMENT PLAN:

The key to preventing errors that can lead to ADRs is prudent, safe prescribing. Any potential negative effects should be taken into account and mitigated in treatment approaches.[11] For instance, prescribing folic acid together with methotrexate will lessen the likelihood of side effects related to folate deficiency, and monitoring electrolytes and renal function when using diuretics or medications with renal activity. These examples can all help to avoid treatment-related side effects, but their applicability may be restricted because monitoring suggestions are frequently insufficient or unclear. It is crucial to keep in mind that careful prescribing may potentially result in a complete avoidance of medication use, and the treatment strategy should always take nonpharmacological or conservative choices into account.

In order to lower the risk of an ADR and stop such "avoidable" reactions from happening in practise, it is necessary to take a systems approach that incorporates a variety of tactics and involves the patient as well as all other healthcare personnel.[12]

DIAGNOSING ADVERSE DRUG REACTIONS:

ADRs are among the best mimics in medicine, frequently mimicking "conventional diseases" and presenting in all bodily systems. Weakness or drowsiness, biochemical or haematological disturbances (such as acute kidney injury, electrolyte imbalance, or anaemia), bleeding, gastrointestinal disturbances, hypoglycaemia, or healthcare-associated infections like Clostridium difficile are just a few ways that drug-related issues in hospitalised patients may manifest. Rarer signs, such as drug-induced lupus, fixed drug eruptions, drug-induced eosinophilia, or drug-induced angioedema, call for greater caution and suspicion on the part of the doctor, who must work diligently to pinpoint the culprit. In order to discover any potential link between the presenting complaint or any subsequent findings and an ADR and to stop more ADRs, a thorough medication history is essential. Several factors can aid in establishing the causality of a specific medicine (Table 2).[13]

In rare circumstances, particular investigations can help with the identification of an ADR by supplying concrete proof of the reaction and reaffirming a drug-induced illness. For instance, organ-specific harm accompanied by drug or metabolite accumulation in intracellular tissue (such as indinavir crystalluria and nephropathy).[14]

Table 1. Examples of pharmacogenetic susceptibility for drug-specific adverse drug reactions.

Drug/drug class	**Pharmacogenetic marker**	**Additional susceptibility factors**	**Example of clinical context**
Carbamazepine	HLA B*15:02 (in the populations listed)	Han-Chinese, Thai and Malaysian populations	Marker for carbamazepine-induced Stevens Johnson syndrome and toxic epidermal necrolysis
Simvastatin	SLCO1B1 (solute carrier organic anion transporter 1B1)	Advanced age, untreated hypothyroidism, excess physical activity, concomitant medications (eg fibrates)	Statin-induced rhabdomyolysis (rare) whose risk is four times greater with single defective allele, 16 times greater with two defective alleles
Abacavir	HLA-B*57:01	Higher CD8 cell count at start of therapy	Marker for abacavir-induced hypersensitivity reactions with fever, rash, lethargy and abdominal and acute respiratory symptoms
Thiopurines (Azathioprine and mercaptopurine)	TPMT activity	N/A	1 in 10 individuals are heterozygous (50% normal TPMT activity) and 1 in 300 have completely deficient activity. Thiopurine-induced myelosuppression is associated with TPMT activity.
N/A = not applicable; TPMT = thiopurine methyl transferase			

Table 2. Medication history elements that may assist clinical assessment of adverse drug reaction (ADR) probability.

Question	Clinical relevance
Have you taken the medication before without adverse effects?	Prior drug exposure doesn't entirely rule out an ADR, although tolerating treatment previously may make hyper-susceptibility reactions less likely
Did anything else change around the time of possible ADR other than the suspected drug (eg other treatments, over the counter medicines, disease progression)	Examination of whether there are alternative causes (other than the suspected drug) that could on their own have caused the reaction
Did the reaction occur only after the drug was started?	While not all ADRs occur immediately or early in therapy (i.e. on drug challenge), an effect occurring before drug exposure is good counter evidence
Did the reaction resolve when the drug was stopped (or when a specific treatment was given)?	Effects that disappear when treatment is stopped (de-challenge) may increase suspicion of an ADR unless an irreversible reaction
Was there ever intentional or accidental use of the drug following an ADR?	An ADR occurring on re-exposure to a drug increases the probability of a causal relationship
Based on original criteria described by Naranjo et al (1981).	

PHARMACOVIGILANCE:

The research and practises involved in the identification, evaluation, comprehension, and avoidance of adverse events or any other drug-related issue are referred to as pharmacovigilance.[15]

In order to promote good vigilance practises for pharmaceutical businesses and the medicines regulators, new law was introduced in the European Union in 2012. The duties and obligations of pertinent stakeholders in terms of medication safety are distinctly defined by this new guidance. A programme of more thorough surveillance for new pharmaceutical drugs and biological agents with black triangle status has been added to the guidance, which is noteworthy (ie those requiring additional monitoring).

One of the guiding ideas is that the risk management policy's proactive methods should take the place of its earlier reactive ones.

REPORTING OF ADVERSE DRUG REACTIONS:

Spontaneous reporting programmes, such as the UK's Yellow Card Scheme run by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines, have been the mainstay of identifying probable ADRs for the past 50 years (CHM). In the wake of the thalidomide catastrophe in the late 1950s, the scheme was established in 1964.

The programme gathers information on alleged adverse drug reactions (ADRs) associated with all prescription and over-the-counter medications and vaccines that are licenced and unlicensed. Only four pieces of information are necessary for a report to be considered valid: an identifiable patient, a reaction, a suspected medicinal product, and an identifiable reporter. Reporters are urged to give assessors as much information as they can, including extra statistics and clinical context.

The UK programme still receives over 25,000 reports annually and gives the drug regulators insight into the frequency of ADRs. Unfortunately, less than 5% of all ADRs are thought to be recorded in practise, making underreporting a persistent problem. This limits the ability of systems to give accurate incidence data. In 2014, NHS England and the MHRA issued a joint alert: Improving medication error incident reporting and learning . As part of this, ADRs occurring as a result of medication errors reported to the National Reporting and Learning System (NRLS) will automatically be reported to the Yellow Card Scheme.

Patients are becoming more involved in their own therapeutic management, and since an early evaluation of patient Yellow Card reporting demonstrated the effectiveness of this strategy,[16] all patients are now actively urged to report adverse drug reactions. Online reporting tools or the use of the Yellow Card app have mostly replaced paper reports (on the original yellow cards). Additionally, integrated reporting that transmits data on ADRs directly to central authorities for processing before entry into national and international databases can be found in electronic health records used in general practise and in some hospitals.

Despite being commonly used for pharmacovigilance, spontaneous reporting systems work best when adverse events are uncommon and rare (affecting less than 1% of treated patients) and when they are indicative of a drug-induced disease (e.g. erythema multiforme). Their application is more restricted to detecting a slight increase in the frequency of frequent occurrences like myocardial infarction or stroke. Due to this, recent drug safety controversies involving thiazolidinedione- and rofecoxib-induced cardiovascular events went unreported despite the fact that these drugs were widely used.

Modern signal generation, albeit outside the purview of this article, can identify early possible damage signals and warn clinicians of potential new therapeutic hazards. Complex statistical data-mining methods are frequently used to find these signals, but they typically need to be further evaluated before being put into practise. It is possible to confirm or deny the existence of potential signals by looking at drug exposure and potential adverse events in databases like the Clinical Practice Research Datalink (CPRD), which is a database of anonymized longitudinal UK primary care records.

Additionally, official drug safety studies, published data, data from periodic safety update reports (PSURs) from pharmaceutical companies, and shared international data are all used in pharmacovigilance. The ability of other "big data" sources, including social media, to identify early signs, however, is also being investigated by regulators and researchers; this is a fascinating and mostly untapped field of study.

MANAGING ADVERSE DRUG REACTIONS:

ADRs are typically managed in practise by changing a dosage schedule or stopping a medication that is thought to be the source of an ADR. However, it's possible that each doctor will choose a different approach to managing an ADR. A strong risk management strategy from the marketing authorization holder, which may include the development of particular treatments for controlling certain ADRs as well as ongoing safety trials, is now required by EU law for all new medications that are approved for sale. Antidotes for directly caused by oral anticoagulant-induced bleeding have demonstrated this. Table 3 provides this and other noteworthy instances of methods for managing particular ADRs.

CONCLUSION:

The detection, management, and reporting of ADRs have been covered in this article. We have discussed how the use of current technology is altering how ADRs are anticipated, avoided, identified, and managed, as well as how we are constantly working to enhance these procedures. As more phenotypic data can be merged to provide prescribers with patient-specific recommendations, individualised therapy is becoming increasingly feasible. Through the lifecycle of a pharmaceutical product, such regulatory science at the national and international levels can assist in achieving a favourable benefit-to-harm ratio. Since avoiding or reducing the risk of ADRs continues to provide a barrier to our routine clinical practise, gaining the optimal results from medicines remains an important priority for individual physicians.

Table 3. Examples of agents used in the management of specific adverse drug reactions.

Specific treatments	Drug/drug class causing ADR	Clinical effect of treatment	Clinical context
Naloxone	Opioids	Antidote for opioid toxicity	Widely used for treatment of overdosage with opioids in a non-medical setting and reversal of postoperative respiratory depression
Icatibant	ACE inhibitors	Treatment for life-threatening angioedema affecting airway/ head and neck	This selective bradykinin B2 receptor antagonist has proven to reduce the time to complete resolution of angioedema
Idarucizumab	Dabigatran	Antidote for the reversal of direct oral thrombin inhibitor	Novel humanised monoclonal antibody fragment developed as specific reversal agent, promptly restoring dabigatranprolonged coagulation parameters to baseline values
Intravenous lipid emulsion (Intralipid®)	Local Anaesthetics (eg lidocaine)	Treatment for systemic toxicity from local anaesthetic agents (eg severe cardiotoxic effects)	Reduce adverse effects resulting from inadvertent local anaesthetic overdoses, intravascular injections, or rapid absorption effects from injections in highly vascular sites
ACE = angiotensin-converting enzyme; ADR = adverse drug reaction			

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