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REVIEW ARTICLE

Principles and mechanisms of Adverse Drug Reaction – A narrative review

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ABSTRACT

Adverse drug reactions (ADRs) continue to be a problem in contemporary medicine, especially in light of growing multimorbidity, ageing populations, and more sophisticated therapies. In addition to examining issues with ADR management, reporting, diagnosis, and prevention in modern clinical practise, this page provides a summary of some of the most important information concerning them.

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

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INTRODUCTION

An adverse drug response (ADR) is defined as "a significantly detrimental or undesirable effect resulting from a measure related to the use of a medicinal product." According to the definition, adverse effects often indicate a risk associated with continued use of the medication and call for its withdrawal, modification of the dosing schedule, prevention, or special treatment. [1] In addition to the authorized use of a medical substance in regular dosages, the term has expanded since 2012 to encompass responses that arise from mistakes, abuse, or misuse as well as suspected reactions to unlicensed or off-label medications. In clinical practice, this change should not have an impact on our strategy to treating adverse drug reactions (ADRs), even if it may influence the reporting and surveillance that manufacturers and pharmaceutical regulators do. Important studies conducted in the United States and the United Kingdom in the 20th centuries revealed that adverse drug reactions (ADRs) are often observed in clinical settings, often leading to unplanned hospital admissions, developing throughout hospital stay, and presenting symptoms following 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 ADR incidence is still present. mostly stable over time. As is always the case, the number of occurrences and the methodology employed to find them are correlated, and most ADRs don't result in significant systemic effects. Nevertheless, because of the related morbidity and mortality, potential financial burden, and possible injury to the prescriber-patient relationship, this frequency of potential harm has to be carefully examined. Certain medications, such as anticoagulants, immunosuppressants, antiplatelets, cytotoxics, diuretics, antidiabetics, and antibiotics, have been linked specifically to hospital admissions attributable to adverse drug reactions. When fatal adverse drug reactions (ADRs) do occur, they are frequently linked to bleeding, with antithrombotic/anticoagulant medications given concurrently with non-steroidal anti-inflammatory drugs (NSAIDs) being the most frequently suspected cause [7].

Classification of ADR [8]

Adverse Drug Reaction is classified in to 2 types –

Type A reactions	Occasionally known as "dose-dependent" and predicted increased effects because of the drug's pharmacology
Type B reactions (bizarre reactions)	which, based on the pharmacology, are peculiar and unpredictable

This basic classification, though still frequently used, is not appropriate for all adverse drug reactions (ADRs). For example, it does not account for chronic side effects linked to cumulative drug exposure or withdrawal reactions (such as rebound hypertension with centrally acting antihypertensive cessation). 'DoTS' is an alternate and possibly more thorough categorization method that groups responses according to the drug's dose, the reaction's time course, and any pertinent susceptibility variables (such as genetic, pathological, and other biological characteristics)[9]. DoTS has the benefit of being useful for diagnosing and preventing ADRs in practice in addition to categorizing responses.

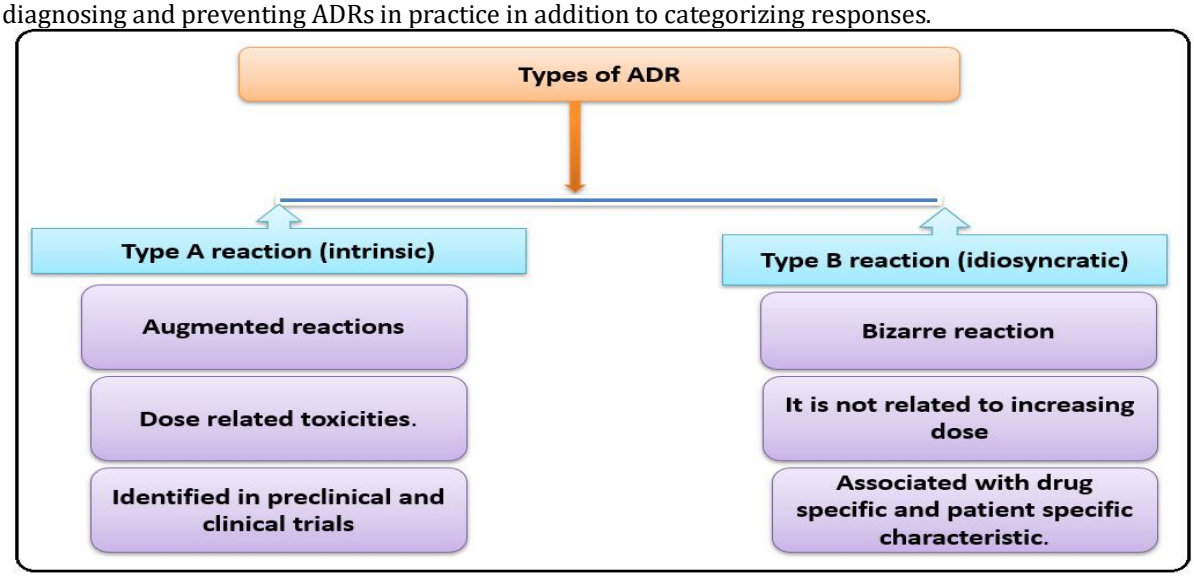

Figure 1. Classification of ADR

Prevention of adverse drug reactions

While certain adverse drug reactions (ADRs) are unpredictably occurring, such anaphylaxis in a patient following a single unremarkable exposure to an antibiotic containing penicillin, many may be avoided with sufficient planning and observation. Preventability, also known as avoidability, is the term used to describe situations in which a drug treatment plan is either impractical when considering known conditions or contradictory with current evidence-based practice. [10] According to epidemiological research, between one-third and one-half of ADRs are (at least possibly) avoidable; nonetheless, it is far simpler to identify preventability in retrospect. Reducing the likelihood of an adverse drug reaction (ADR) can, however, be a significant strategy for lowering the risk of patient injury. There are two fundamental actions that may be taken to stop an ADR from happening.

- Determine which patient subgroup is most likely to have the negative impact and adjust the course of therapy accordingly.
- Make sure the treatment strategy minimizes any potential side effects.

Identifying susceptibility

Understanding the susceptibilities of your patients can help you prescribe less and lower the chance of an adverse drug reaction. Any prior ADRs will be identified by a patient's medication history, preventing re-exposure to the drug. In other situations, risk variables for adverse drug reactions (ADRs) might be used to estimate the likelihood of an event. For instance, due to the possibility of ACE inhibitor-induced angioedema, guidelines recommend that pharmacogenetics, which predicts who is more likely to have a certain ADR, is beginning to produce more individualized medication options (Table 1).

Table 1 - Examples of pharmacogenetic susceptibility for drug-specific adverse drug reactions. (N/A = not applicable; TPMT = thiopurine methyl transferase)

Drug Name	Pharmacogenetic marker	Susceptibility factors	Example
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.

At the point of care, clinical decision support systems can notify clinicians of any patient-specific treatment warnings or further monitoring needs to lower the risk of damage. Although a thorough analysis is outside the purview of this work, practitioners shouldn't rely only on decision support since systems differ greatly in the information they provide, ranging from a lack of pertinent warnings to an abundance of information that causes alert fatigue.

Treatment plan

Prescribe carefully and sensibly to minimize mistakes that might lead to adverse drug reactions. Plans for treatment should take into account and minimize any potential negative effects. [11] For instance, co-prescribing folic acid together with methotrexate can lower the likelihood of folate deficiency-related side effects. It can also help to monitor electrolytes and renal function while using diuretics or other renally active medications. All of these examples can stop side effects from therapy from occurring, but their applicability may be restricted since monitoring guidelines are frequently unclear or insufficient. It's crucial to keep in mind that conservative or non-pharmacological solutions should always be considered in the treatment plan, and careful prescription may help prevent medication usage entirely. To lower the likelihood of an ADR and stop such "avoidable" responses from happening in practice, a systems approach incorporating several techniques, the patient, and all healthcare workers is needed [12](Figure 2).

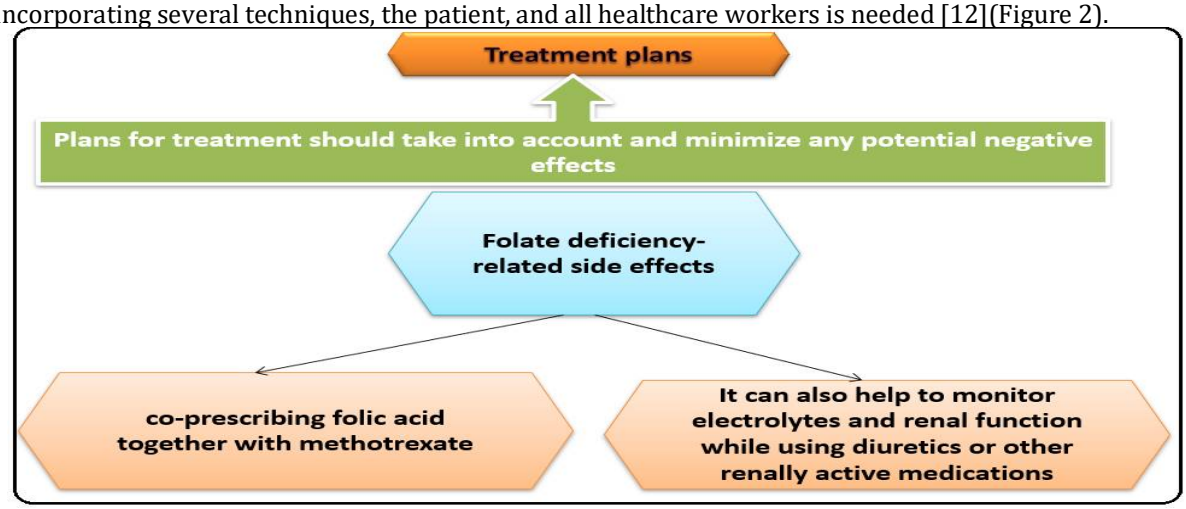

Figure 2. Treatment Plan

Diagnosis of adverse drug reactions (Figure3)

One of the greatest imitators in medicine is ADRs; they frequently imitate "traditional diseases" and show up in all bodily systems. Admitted patients experiencing drug-related complications can manifest in a variety of ways, such as fatigue or weakness, anemia, bleeding, gastrointestinal disorders, hypoglycemia, or infections linked to healthcare, such as Clostridium difficile. They can also present as biochemical or

haematological abnormalities. Less common signs, from the doctor, who should work extremely hard to determine the cause. In order to discover any potential link between the presenting complaint or any later findings and an ADR and to stop more ADRs, a thorough medication history is essential. Certain examinations, by verifying a drug-induced sickness and offering objective proof of the reaction, can help diagnose an adverse drug reaction (ADR) in certain circumstances. For instance, organ-specific harm combined with drug or metabolite deposition inside cells (e.g., indinavir crystalluria and nephropathy). Certain examinations, by verifying a drug-induced sickness and offering objective proof of the reaction, can help diagnose an adverse drug reaction (ADR) in certain circumstances. For instance, organ-specific harm combined with drug or metabolite deposition inside cells (e.g., indinavir crystalluria and nephropathy) [13,14].

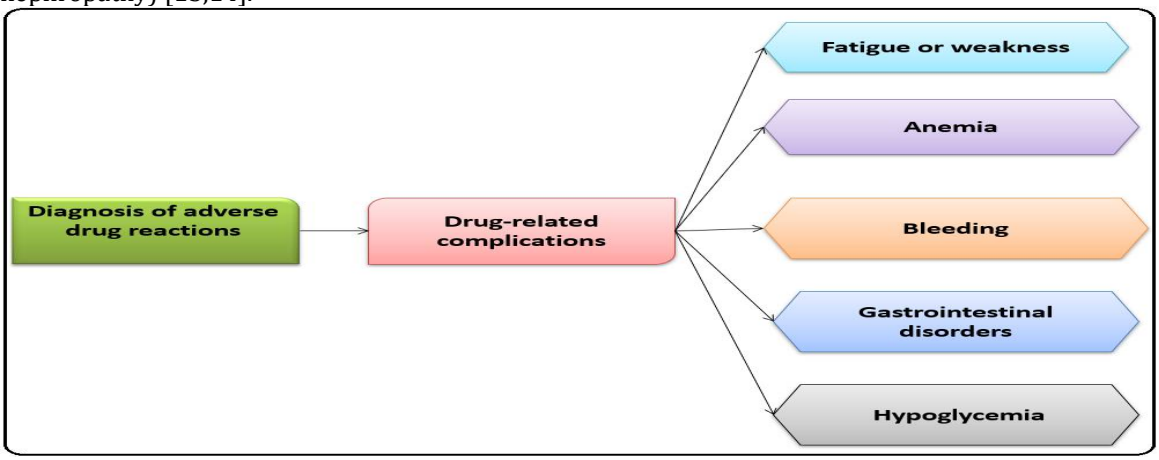

Figure 3. Diagnosis of Adverse Drug Reactions

Concept of Pharmacovigilance

"Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse events or any other drug-related problem" [15]. In 2012, new law was adopted in the European Union to guarantee pharmaceutical businesses and medication regulators effective vigilance practices. The duties and obligations of pertinent stakeholders with regard to drug safety are clearly defined in this new advice. Significantly, a program of more thorough surveillance for newly discovered pharmaceuticals has been implemented by the guidelines. One of the tenets is that the risk management policy's proactive techniques take the place of the earlier reactive ones.

Reporting process of adverse drug reactions

For the past 50 years, mechanisms for voluntary reporting, including the UK's Yellow Card Scheme have been the cornerstone for identifying possible adverse drug reactions. In the wake of the thalidomide debacle in the late 1950s, the system was established in 1964. The program gathers information on suspected adverse drug reactions (ADRs) associated with all legal and unlicensed medications and vaccines, including those that are prescribed or bought over-the-counter, by self-reporting. Only four pieces of information are needed for a report to be considered valid: an identifying reporter, a response, a suspected medical substance, and an identifiable patient.

Reporters are urged, meanwhile, to give assessors as much information as they can, including further statistics and clinical context. The UK program still receives about 25,000 reports annually, which gives medical regulators information on the incidence of adverse drug reactions. Sadly, underreporting is still a major problem; it is believed that less than 5% of all ADRs are actually recorded. This restricts the systems' capacity to provide precise incidence statistics. A joint alert on improving medication mistake incident reporting and learning was released in 2014 by NHS England and the MHRA. This includes automatically reporting to the Yellow Card Scheme any adverse drug reactions (ADRs) that arise from medication mistakes.

Patients are taking an increasingly active role in their own treatment management. All patients are being actively encouraged to report adverse drug reactions (ADRs) because an early evaluation of Yellow Card reporting by patients demonstrated the effectiveness of this strategy [16]. Online reporting tools and using the Yellow Card app have mainly integrated reporting, which transmits data on ADRs immediately to central authorities for processing before to inclusion into national and international databases, is another feature of electronic health records utilized in general practice and in certain hospitals. Although

spontaneous reporting methods for pharmacovigilance are often used, they work best when adverse events are infrequent and they are indicative of a drug-induced illness (such as erythema multiforme). Their applicability is more constrained when detecting a little rise in the incidence of typical events, such stroke or myocardial infarction. This explains why recent drug safety controversies, including the cardiovascular events caused by rofecoxib and thiazolidinedione, were unreported despite these drugs' widespread usage. Modern signal generation can identify early possible indications of damage and notify doctors of potential new treatment hazards; however, this is outside the purview of this article. In order to find these signals, sophisticated statistical data-mining methods are frequently used; nevertheless, taking any action typically requires additional evaluation first. The existence of such signals can be confirmed or denied by looking up drug exposure and possible adverse events in databases, which is an anonymized longitudinal collection of primary care records in the UK. Pharmacovigilance employs a wide range of additional techniques and data sources, such as published data, shared international data, data from pharmaceutical companies' reports, and formal drug safety studies. Regulators and scientists are now investigating, though, if other "big data" sources, including social media, might identify early warning signs; this is still an intriguing and mostly uncharted field of study (Figure 4).

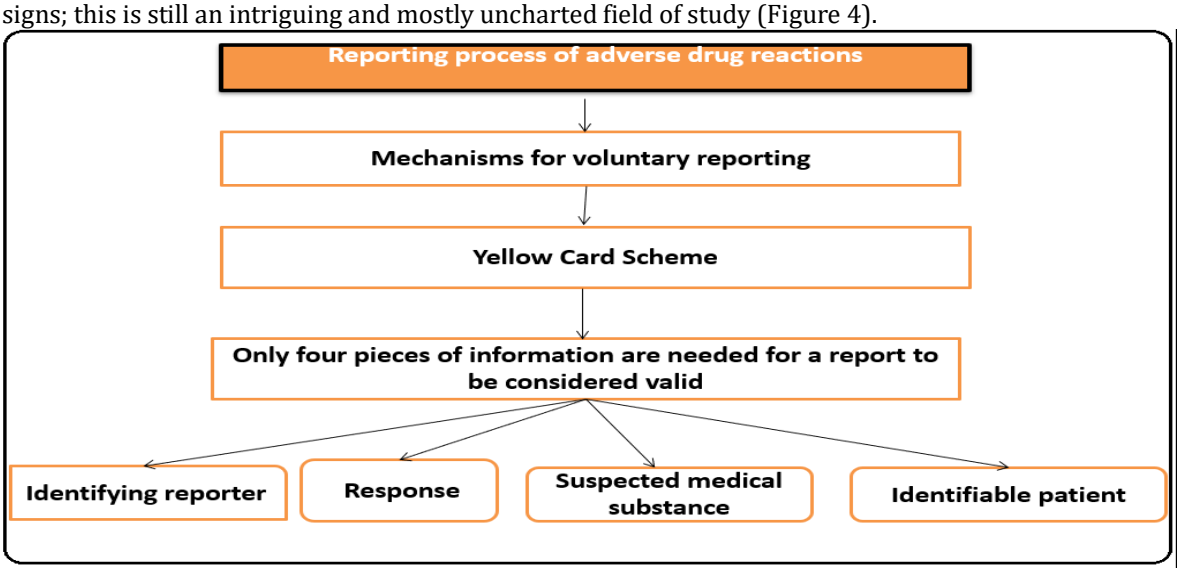

Figure 4 Reporting Process of Adverse Drug Reactions

Management Strategy for Adverse Drug Reaction

In reality, addressing adverse drug reactions (ADRs) sometimes involves changing a dose schedule or stopping a medication that may be the cause of an ADR. However, each clinician will probably follow a different path while managing an ADR. A comprehensive risk management strategy from the marketing authorization holder, which may include continuing safety trials and the development of particular therapies for controlling certain ADRs, is now required by EU regulation before any new medications are approved for sale. Antidotes for bleeding caused by direct oral anticoagulant ingestion have demonstrated this.

CONCLUSION

We have covered ADR identification, administration, and reporting in this section. We have discussed how ADR prediction, prevention, detection, and management are being altered by contemporary technology and how we are still working to make these processes better through further technical advancements. With the ability to combine phenotypic data with pharmacogenetics to provide prescribers with patient-specific recommendations, individualized treatment is becoming increasingly feasible. Throughout a pharmaceutical product's lifespan, such regulatory science at the national and international levels can assist in achieving a good benefit-to-harm ratio. Because preventing or reducing the risk of adverse drug reactions (ADRs) continues to be a difficulty in our daily clinical practice, attaining the greatest possible results from medicines remains a top priority for individual physicians.

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