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A REVIEW ON ADVERSE DRUG REACTION AND IT'S TYPES WITH THEIR MANAGEMENT

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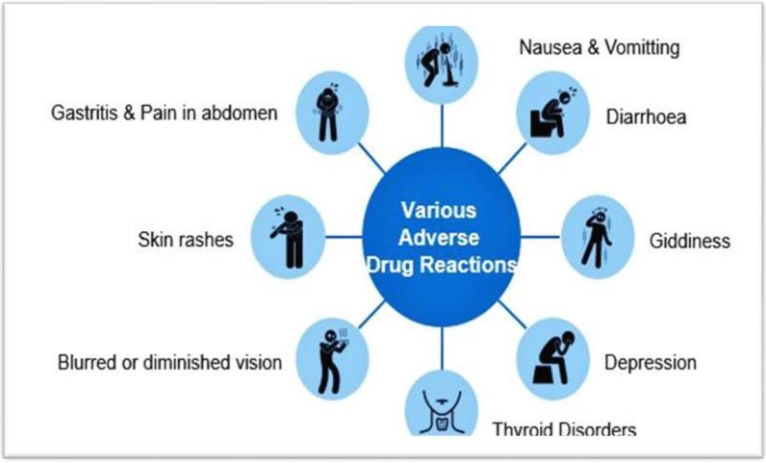
➢ INTRODUCTION

- An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use. Adverse drug reactions occur almost daily in health care institutions and can adversely affect a patient's quality of life, often causing considerable morbidity and mortality. Much attention has been given to identifyingthe patient populations most at risk, the drugs most commonly responsible, and the potential causes of ADRs. An increase in the number of drugs on the market, an aging population, and an upward trend in polypharmacy are contributing factors of ADRs worldwide
- Adverse drug reactions (ADRs) – unintended, harmful events attributed to the use of medicines – occur as a cause of and during a significant proportion of unscheduled hospital admissions
- An adverse drug reaction is any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use. In contrast, an adverse drug event is an untoward occurrence after exposure to a drug that is not necessarily caused by the drug.

KEYWORDS: Adverse drug reactions, clinical pharmacology, drug related side effects and adverse reactions, pharmacovigilance, adverse drug reaction reporting system.



- When a drug is marketed little is known about its safety in clinical use because only about 1500 patients are likely to have been exposed to it Thus drug safety assessment should be considered an integral part of everyday clinical practice since detection and diagnosis often depend on clinical acumen.

- Adverse drug reactions may cause patients to lose confidence in orhave negative emotions toward their physicians and seek self- treatment options, which may consequently precipitate additionalADRs.

- Around 5% of all hospital admissions are the result of an ADR, and around 10%– 20% of inpatients will have at least one ADR during their hospital stay (Kongkaew 2008; Lundkvuist 2004; Pirmohamed 1998).

- The actual incidence of ADRs may be even greater

because some ADRs mimic natural disease states and may thus go undetected and/or unreported. Although some ADRs present as minor symptoms, others are serious and cause death in as many as 0.1%–0.3% of hospitalized patients (Lazarou 1998; Pirmohamed 1998).

- Adverse drug reactions should be quickly identified and managedto limit their detrimental effects on the patient

- The most commonly used definition of an ADR is a response to a drug that is 'noxious, unintended and occurs at doses normally used in man'. This definition arose from the World Health Organization (WHO) report on International Drug Monitoring in 1972, and remains largely unchanged.

- Importance of adverse drug reactions Adverse drug reactions:

- Account for 5% of all hospital admissions o Occur in 10-20% ofhospital inpatients
- Cause deaths in 0.1% of medical and 0.01% of surgical inpatients o Adversely affect patients' quality of life o Causepatients to lose confidence in their doctors o Increase costs of patient care o Preclude use of drug in most patients, although they may occur in only a few patients
- May mimic disease, resulting in unnecessary investigations anddelay in treatment

➢ OBJECTIVES OF ADR

The objective of monitoring and managing adverse drug reactions (ADRs) is to ensure patient safety, improve therapeutic outcomes, and minimize harm associated with medication use. This involves:

1. Identifying ADRs to understand their nature and frequency.
2. Assessing the risk factors and potential causes of ADRs.
3. Reporting ADRs to regulatory authorities to enhance pharmacovigilance.
4. Implementing strategies to prevent or mitigate ADRs through education and revised treatment plans.
5. Improving drug development and labeling by integrating findings into clinical guidelines.

➢ CLASSIFICATION OF ADR

Adverse drug reactions were originally classified into two subtypes. Type A ADRs are dose-dependent and predictable; they are augmentations of known pharmacologic effects of the drug, such as orthostatic hypotension with antihypertensive medications. Type B ADRs are uncommon and unpredictable, depending on the known pharmacology of the drug; they are independent of dose and affect a small population, suggesting that individual patient host factors are important (Pirmohamed 2003; Edwards'2000).

- Hypersensitivity (allergic) reactions to drugs are examples of type B ADRs. Type A reactions were later called augmented, andtype B reactions, bizarre. Two further types of reactions were eventually added: chronic reactions, which relates to both dose and time (type C), and delayed reactions (type D). Withdrawal later became the fifth category (type E), and most recently, unexpected failure of therapy became the sixth (type F) (Rohilla 2013; Edwards 2000).

- About 80% of ADRs in the hospital setting or causing admission to a hospital are type A (Pirmohamed 1998). These ADRs are potentially avoidable and often predictable. The drug classes most commonly responsible for ADRs in adults are adrenal corticosteroids, antibiotics, anticoagulants, antineoplastic and immunosuppressive drugs, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, and opiates. For children, the most prevalent drug classes for ADRs are anti-infective drugs, respiratory drugs, and vaccine

- **Types of Adverse Drug Reactions**

1. Type A (Augmented) Reactions

- Description: Predictable and dose-dependent effects resulting from the pharmacological action ofthe drug.
- Examples: Excessive bleeding from anticoagulants, hypotension from antihypertensive.
- Management: Dose adjustment, careful monitoring, and patient education.

2. Type B (Bizarre) Reactions

- Description: Unpredictable and not dose-dependent; oftenrelated to individual patient characteristics.
- Examples: Allergic reactions, anaphylaxis, idiosyncratic reactions (e.g., Stevens Johnson syndrome).
- Management: Immediate discontinuation of the drug, supportive care, and administration of antihistamines or corticosteroids if necessary.

3. Type C (Chronic) Reactions

- Description: Related to long-term drug therapy and cumulative effects.
- Examples: Osteoporosis from long-term corticosteroiduse, renal impairment from NSAIDs.
- Management: Regular monitoring, adjusting therapy, and preventive measures (e.g., bisphosphonates for osteoporosis).

4. Type D (Delayed) Reactions

- Description: Occur after a delay, often after prolonged exposure to the drug.
- Examples: Carcinogenic effects of certain chemotherapeutics, teratogenic effects during pregnancy.
- Management: Patient education about long-term risks, regular screenings, and counselling for family planning.

5. Type E (End of Treatment) Reactions

- Description: Reactions that occur upon withdrawal of a drug.
- Examples: Withdrawal symptoms from opioids orbenzodiazepines.
- Management: Gradual tapering of the medicationand supportive care.

6. Type F (Failure) Reactions

- Description: Treatment failure due to inadequate response or drug interactions.
- Examples: Sub therapeutic dosing or antagonistic effects from polypharmacy.

Management: Review of the drug regimen, dose adjustments, or switching to alternative therapies.

➢ **FACTTORS AFFECTING ADR**

1. Pharmacological Factors

A. Drug Properties

- Chemical Structure: Certain chemical classes are more likely to cause specific reactions (e.g., sulphonamides causing allergic reactions).
- Dosage: High doses can lead to toxicity, while low doses may be ineffective, potentially causing frustration or non-compliance.
- Route of Administration: Different routes (oral, intravenous, etc.) can influence absorption and effects.

B. Drug Interactions

- Polypharmacy: The use of multiple drugs increases the risk of interactions, leading to potentiation or antagonism of effects.
- Common Interactions:
- Warfarin and NSAIDs (increased bleeding risk)
- Antibiotics and oral contraceptives (reduced effectiveness)

2. Patient Factors

A. Genetic Factors

- Genetic variations can significantly affect drug metabolism. For example, polymorphisms in cytochrome P450 enzymes can lead to differences in drug processing and toxicity.
- Example: Individuals with variations in the CYP2D6 enzyme may experience either increased toxicity or reduced efficacy from drugs metabolized by this pathway.

B. Age

- Elderly Patients: Age-related physiological changes affect drug absorption, distribution, metabolism, and excretion, leading to increased ADR risk.
- Paediatric Considerations: Children metabolize drugs differently than adults, necessitating careful dosing.

C. Gender

- Hormonal Influences: Differences in hormonal levels can affect drug metabolism and efficacy, potentially leading to varied ADR experiences between genders.

D. Comorbidities

- Chronic Conditions: Patients with multiple health issues may be prescribed several medications, increasing the risk of ADRs due to interactions or overlapping side effects.

3. Environmental Factors

A. Diet and Lifestyle

- Food Interactions: Certain foods can alter drug absorption and metabolism (e.g., grapefruit juice affecting statin metabolism).
- Lifestyle Choices: Alcohol and smoking can exacerbate drug effects or lead to adverse outcomes.

B. Socioeconomic Status

- Access to Healthcare: Patients with limited access may struggle with medication management and adherence, increasing the likelihood of ADRs.
- Health Literacy: Understanding medication instructions and side effects is crucial for adherence and safety.

4. Drug Administration Issues

A. Dosing Errors

- Calculation Mistakes: Errors in calculating dosages can lead to under dosing or overdosing, both of which can result in ADRs.
- Complex Regimens: Complicated dosing schedules can lead to confusion and mistakes.

B. Formulation Issues

- Excipients: Inactive ingredients can cause reactions in sensitive individuals, highlighting the importance of formulation in drug safety.

5. Immunological Responses

A. Allergic Reactions

- Type I Reactions: Immediate hypersensitivity reactions can lead to anaphylaxis, urticarial, or asthma.
- Type IV Reactions: Delayed hypersensitivity can cause skin reactions or other systemic effects.

B. Idiosyncratic Reactions

- Unpredictable Responses: These reactions are often unrelated to drug dosage or pharmacological properties and can be challenging to predict.

6. Duration of Therapy

- Cumulative Effects: Prolonged exposure to certain drugs (e.g., corticosteroids) can lead to long-term ADRs, such as osteoporosis or adrenal suppression.
- Withdrawal Effects: Abrupt discontinuation of medications can result in rebound effects, leading to new health issues.

7. Patient Adherence

❖ **Non-compliance**

- Reasons for Non-compliance: Complexity of regimens, side effects, or lack of understanding can lead to patients not taking medications as prescribed.
- Consequences: Non-adherence can result in treatment failure or exacerbation of underlying conditions.

➢ **MANAGEMENT OF ADR**

1. Identification and Monitoring

- Vigilant Assessment: Healthcare providers should conduct thorough assessments to identify potential ADRs, particularly during initial treatment phases and after dosagechanges.
- Use of Scales: Tools like the Naranjo Scale can help determine the likelihood of an ADR being related to a medication.

2. Reporting and Documentation

- Adverse Event Reporting: Encourage healthcare professionals to report ADRs to national databases (e.g., FDA's Med Watch) for ongoing safety monitoring.
- Patient Records: Documenting ADRs in patient records helps inform future prescribing and alerts other providers.

3. Patient Education

- Informed Consent: Educate patients about potential ADRsbefore starting new medications, emphasizing the importance of reporting any unusual symptoms.
- Clear Communication: Provide written materials that outline common side effects and what to do if they occur.

4. Modification of Therapy

- Dose Adjustment: If an ADR is suspected, consider adjusting the dosage or switching to an alternative medication with a better safety profile.
- Drug Discontinuation: In severe cases, immediate discontinuation of the offending drug may be necessary.

5. Supportive Care

- Symptomatic Management: Provide treatments to alleviate symptoms caused by ADRs, such as antihistamines for allergic reactions or antiemetic's for nausea.
- Monitoring: Close monitoring may be required for patients experiencing significant ADRs to ensure safety and address complications.

6. Multidisciplinary Approach

- Team Collaboration: Engage pharmacists, nurses, and other healthcare professionals to assess and manage ADRs effectively. A multidisciplinary approach can enhance patientcare and safety.

7. Preventive Strategies

- Pharmacogenomics: Utilize genetic testing to identifypatients at risk for specific ADRs, allowing for more personalized medication management.
- Medication Reconciliation: Regularly review and reconcile medications during transitions of care (e.g., hospital admissions and discharges) to prevent ADRs related to drug interactions.

8. Surveillance

- Outsides of formal surveillance systems, all health-care professionals have a responsibility to inform their colleagues about clinically important adverse drug reactions that they detect, even if a well-recognised or causal link is uncertain.
- Information on what has happened and how the diagnosis has been made should be forwarded to a national centre with responsibility for giving general information about drugs and for taking regulatory action. National centres send this information to the WHO worldwide database.
- This global information is analysed by the WHO Collaborating Centre for International Drug Monitoring (theUppsala

Monitoring Centre), now with artificial intelligence in the form of a Bayesian Confidence Propagation Neural Network, which allows the analysis of all the variables in a report against the background information contained in the WHO database of over 2 million reports.

9. Strategy to improve drug safety

- Avoidance of chemical functional groups that are well recognised to cause toxicity during drug design for example, aromatic amines, phenols, epoxides, and Quinones
- Development of metabolically inert drugs to avoid metabolic interactions and prevent formation of toxic metabolites—for example, vigabatrin and gabapentin
- Development of suitable in vitro and in vivo systems to elucidate the role of short lived, potentially toxic metabolites in the pathogenesis of idiosyncratic toxicity
- Increased use of in vitro systems. Such as cell lines expressing drug metabolising enzymes, to predict the potential for adverse drug interactions and polymorphic routes of metabolism
- Study of high risk patients during the premarketing drug development phase to identify pharmacokinetic and pharmacodynamics factors that influence susceptibility to drugtoxicity

o Development of computer based schemes to monitorfor adverse reactions and adverse events in primary and secondary care

- Encouragement to report adverse drug reactions to regulatory agencies
- Identification of risk factors for different types of drug toxicity by using pharmacoepidemiological

approaches
- Identification of multigenetlc predisposing factors to allow the prediction of individual susceptibility.

➢ **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'.
- New legislation was introduced in the European Union in 2012 to ensure good vigilance practice for pharmaceutical companies and the medicines regulators. This new guidance clearly identifies the roles and responsibilities of relevant stakeholders in terms of drug safety. Notably, the guidance has introduced a programme of more intensive surveillance for new pharmacological agents and biological agents with black triangle status (ie those requiring additional monitoring). One of the guiding principles is that the pro-active strategies of the risk management policy replace the previous reactive strategies.

❖ **Reporting of adverse drug reactions**
- The mainstay of detecting potential ADRs over the last half a century has been spontaneous reporting systems such as the Yellow Card Scheme in the UK, operated by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM).
- The scheme was founded in 1964 following the thalidomide disaster in the late 1950s. Through spontaneous reporting, the scheme collects data on suspected ADRs related to all licensed and unlicensed medicines and vaccines, including those issued on prescription or purchased over the counter.
- For a report to be valid, only four items of information are required: an identifiable patient, a reaction, a suspected medicinal product and an identifiable reporter. However, reporters are encouraged to provide as much information as possible, i.e. to provide additional data and clinical context for assessors. The UK scheme continues to receivein the region of 25,000 reports per year and provides the medicine regulators an insight into the occurrence of ADRs.
- Unfortunately, underreporting remains a key challenge, with fewer than 5% of all ADRs estimated as being reported in practice. 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 increasingly involved in their own therapeutic management and, because an early assessment of patient Yellow Card reporting proved the value of this approach,[16] all patients are now actively encouraged to report ADRs. Paper reports (on the original yellow cards) have largely been superseded by online reporting systems or use of the Yellow Card app.
- Electronic health records used in general practice and in some hospitals can also include integrated reporting that sends data on ADRs directly to central agencies for processing before entry into national and international databases.

➢ **FUTURE DEVELOPMENTS**
- The work of the WHO monitoring programme in Uppsala is described in detail elsewhere.[21] The programme also supports the European Pharmacovigilance Research Group, which has allowed regulators and drug safety specialists from a variety of European countries to come together to plan coordinated drug-safety exercises.
- Initiatives like these may pave the way for much more logical development and investigation of drug safety signals worldwide.
- Among the developments planned for the WHO programme are:

  - An extension of the method of Bayesian artificial neural networks for the analysis of large amounts of data, in the hope of detecting hitherto unrevealed risk factors for the development of drug-related ailments
  - Improvements in the classification systems of traditional herbalremedies.
  - Methods for improving communications in pharmacovigilance, as setout in the Erice declaration
  - Cooperation with organisations interested in developing early signalsof significance, including the International Society for Pharmacoepidemiology, which is specifically interested in the science of pharmacovigilance, and the Council for International Organizations of Medical Sciences, which is pivotal in bringing interested parties together to mount various collaborative projects.
- Clinical pharmacology has a very exciting future, because of possibilities of interfering with disease processes at ever more basic and specific levels.
- Knowledge of the human genome will allow us to predict susceptibility to an increasing number of diseases, and drug-induced disease will alsobe better understood as we gain knowledge of genetic influences on drug pharmacokinetics and pharmacodynamics: we already use phenotyping and genotyping to predict some drug problems related to drug metabolism.
- Further genomic developments will allow us to develop predictive tests for the actions of drugs, including adverse drug reactions, holding out the possibility of more accurate tailoring of therapy to the individual.
- As we accumulate more and more information on drug responses, we must not lose sight of the

sobering fact that about half the cases of drug-related injury are from potentially avoidable adverse drug reactions.

➢ CONCLUSION

- The importance of adverse drug reactions is often underestimated.
- They are common and can be life threatening and unnecessarily expensive.
- The measures outlined in the box above are important to improve the benefit to risk ratio of drug treatment by reducing the burden of drug toxicity.
- Because of the wide range of drugs available, the manifestations of toxicity may vary and affect any organ system.
- In fact, adverse reactions have taken over from syphilis and tuberculosisas the great mimics of other diseases.
- The pattern of toxicity is likely to change with the introduction of new biotechnology products.
- It is therefore important for prescribing clinicians to be aware of the toxic profile of drugs they prescribe and to be ever vigilant for the occurrence of unexpected adverse reactions.

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