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Open Access Review Article

ADVERSE DRUG REACTIONS: A COMPREHENSIVE REVIEW

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ABSTRACT

Adverse drug reactions are the undesirable unintended response of the drug which occurs at the doses normally used for the diagnosis, prophylaxis and treatment of the patient. ADR is the harmful effect other than desirable or expected which can vary from desirable from mild to severe reaction, even sometimes responsible for causing considerable morbidity and mortality. The reasons include overdose, polypharmacy, diseased condition etc. to name few among them. The increased ADR rate is highly alarming and thus requires proper monitoring and reporting of ADR to the concerned regulatory authorities. In this review we try to cover different aspects of adverse drug reactions like its types, factors affecting ADR, reasons for increasing rate of ADR, preventive measures and also the monitoring and reporting of ADR.

Keywords: Adverse drug reactions, polypharmacy, overdose

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INTRODUCTION

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.[1]

World Health Organization defines ADRs as 'a response to medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function' [2]

"A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration."[3]

The Joint Commission on the Accreditation of Healthcare Organisations (JCAHO) defines an adverse drug reaction (ADR) as an undesired effect of a medication that either increases toxicity, decreases desired therapeutic effect, or both [4,5,6]

As per Edwards ADR is an appreciably harmful or unpleasant reaction, caused by an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.[6,7]

As defined by ASHP Adverse drug reaction is an unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic), enquires changing the drug therapy, requires modifying the dose (except for minor dosage adjustments), necessitates admission to a hospital, prolongs stay in a health care facility,

necessitates supportive treatment, significantly complicates diagnosis, negatively affects prognosis, or results in temporary or permanent harm, disability, or death)[7]

TYPES OF ADVERSE DRUG REACTIONS [3,7,8]

1. Augmented or dose related
2. Bizarre or Non dose related
3. Dose and time related
4. Time related
5. Withdrawal
6. Failure of therapy

1. **Augmented:** Most common and major cause of ADR. It is related to the pharmacological action of drug. It is dose dependent and the level of severity increases with increase in dose. Its occurrence can be limited by slow introduction of low dosages. Predictable by the pharmacological mechanisms, e.g., dry mouth with tricyclic antidepressants and respiratory depression with opoids.
2. **Bizarre**: It is rare, not related to pharmacologic action of drug, also unrelated to the dose, unpredictable, mechanisms are unknown. It can be fatal resulting in high mortality, e.g. aplastic anaemia caused by chloramphenicol, neuroleptic malignant hyperthermia caused by some general anaesthetics and antipsychotics. Management includes withholding the drug avoidance in future.
3. **Dose and Time Related**: Occurs as a result of continuous drug use i.e. cumulative dose. It is umcommon, unexpected & unpredictable, e.g. tardive dyskinesias by antipsychotics, dementia by anticholinergic medications, osteonecrosis of the jaw with bisphosphonates
4. **Time Related:** Delayed occurrence of ADRs, Occurs or becomes apparent sometime after use of the drug even after the cessation of treatment e.g., corneal opacities after thioridazine, ophthalmopathy after chloroquine, leucopenia with lomustine.
5. **Withdrawal:** Withdrawal reactions which are uncommon and occur soon after the withdrawal. Management includes reintroducing the drug and withdrawing it slowly. Occurs typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer; insomnia and anxiety with benzodiazapenes.
6. **Failure of Therapy:** It is common in occurrence, related to dose of drug and interactions between the drugs are the major reason of this type of ADR. Management includes consideration of simultaneous drug therapy.

ADVERSE DRUG EVENT [7]

Any unexpected occurrence that may occur during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the drug in use.

WHY IS THE FREQUENCY OF ADR'S ALARMING?[4]

There are several reasons to which it can be attributed, which include:

1) Polypharmacy; simultaneous administration of various drugs at same time for an individual's patient.
2) Patient non adherence, healthcare provider's workloads, unfamiliarity or ignorance to ADR's and communication failures.
3) The ever-increasing number of new drugs in the market; and,
4) Insufficient attention to identify adverse drug reactions
5) The lack of a defined and systematic approach for monitoring of adverse drug reactions

PREDISPOSING/ SUSCEPTIBILITY FACTORS TO ADVERSE DRUG REACTIONS [7,9,10,11]

They can be categorised as:

1. Patient related factors
2. Drug related factors
3. Disease related factors
4. Social factors

Drug Related Factors

1. **Drug dose, frequency and Time of Administration:** Administering under dose or over dose of medication, increasing or decreasing frequency of administration, changing the appropriate time of the day to administer the medication can cause patient harmful drug effects.
2. **Poly-pharmacy:** It may cause ADRs due to the drug additive effect, synergism, duplication, drug interactions, discontinuation of treatment and physiological antagonism.

Patient Related Factors

1. **Age:** Paediatrics and geriatrics. These categories of patients are not usually studied extensively during clinical trials. Geriatric patients with multiple disease conditions, decreased drug elimination and previous history of allergy are more prone to ADRs. However, paediatric patients have low capacity to metabolize drug hence more prone to ADRs.
2. **Sex:** Men differ from women in GIT motility also have higher body weight, internal organ size and glomerular filtration but lesser body fat; these factors affect both the drug pharmacokinetics and pharmacodynamics. Menstruation, pregnancy and menopause are peculiar to women; their occurrence may significantly affect drug actions.
3. **Pregnancy:** During pregnancy several physiological changes occur which may affect drug pharmacokinetics as well as pharmacodynamics; these include cardiovascular changes; increase in cardiac output (32%) due to the increase in heart rate (10-15bmp) and increase in stroke volume;

increase in blood volume (1500-1800ml); increase in renal drug excretion due to increase in renal blood flow (30%), increase in GFR (50%) and decrease in serum protein (1-1.5) .GIT motility, acidity and tone increase during pregnancy which leads to changes in drug absorption, excretion and metabolism **.**During pregnancy ADRs may affect only the mother, the foetus or both.

4. **Renal function:** Kidney disease alters rate of drug clearance and metabolism leading to drug toxicity and low therapeutic effect which can be diagnosed by level of creatinine clearance.

Disease Related Factors

Drug that is useful in treatment of one disease may be harmful in others; using NSAIDS to treat pain may exacerbate peptic ulcer; also condition of patient with asthma may worsen if he is treated with propranolol for angina or hypertension. Patients with chronic diseases like diabetes, high or low blood pressure, ulcer, glaucoma, an enlarge prostate, poor bladder control should be monitored carefully, because such categories of patients are more prone to drug-disease interaction and ADRs.

Social Factors

1. **Smoking:** Smoking induce liver cytochrome P450 iso-enzymes CYP1A1, 1A2 and possibly 2E2 leading to the increase in metabolism of drugs that are substrate to these group of enzyme and decrease their pharmacological action Studies revealed that cigarette smoking decrease the action of β-blockers on blood pressure. Smoking also interacts with drugs like theophylline, thiothixene, insulin, oral contraceptives, and H**2** blockers. Clinical investigation proves that on average, insulin dependent diabetic smoker needed 15-20% more insulin than non-smokers, and up to 30% more for heavy smokers.
2. **Alcohol**: affect drug metabolism and promote development of ADRs. Alcohol causes hepatitis and liver cirrhosis that significantly affect the rate of drug metabolism; liver disease is proved to increase the toxicity of β-blockers. Concurrent ingestion of alcohol with some drugs has led to many ADRs like nausea, vomiting, headache, drowsiness, fainting, and hypotension.
3. **Race**: Occurrence of ADRs differs from one population of patients to another due to genetic differences Patient from East-Asia have three times risk of developing cough with ACE inhibitors than white patients. Research has shown that black people had higher risk of intracranial haemorrhage and also had 3.0 relative risk of angioedema compared to non-black people.

PREVENTING ADVERSE DRUG REACTIONS [8]

These steps can help in preventing the occurrence of adverse drug reaction:

1. Identification of the group of individuals who are probably more susceptible to the adverse effect and accordingly the modification in the treatment plan.
2. Ensuring that the treatment plan alleviates any possible adverse effects.

Identifying Susceptibility

A patient's medication history helps in identifying any previous ADRs and therefore prevents re-exposure to the drug. Patient's susceptibility accordingly helps in making the decision for prescribing the right drug of choice. As discussed earlier number of factors affects the susceptibility such as age, gender, pregnancy status and racism can help predict the risk of an ADR occurrence.

Treatment Plan

Judicious and safe prescribing plays an important role in reducing errors that can contribute to ADRs. Treatment plans should consider and mitigate for any possible adverse effects. For example, co-prescription of folic acid with methotrexate will reduce the incidence of adverse effects associated with folate deficiency; and monitoring electrolytes and renal function when treating with renally active drugs or diuretics. These examples can all prevent treatment-emergent adverse effects although may be limited because monitoring recommendations are often inadequate or ambiguous.

POPULATIONS AT GREATER RISK [7,10,11]

1. Paediatrics
2. Geriatrics
3. Patients with renal and hepatic impairment
4. Genetic Variations

Pediatrics: Infants and very young children are more susceptible or at a greater risk of ADR since their capacity to metabolize the drug is not fully developed. Neonates have immature renal tubular function below 8 weeks thus NSAIDS are necessarily required to be avoided. Physiologic hypoalbuminemia affects drug dosing. The body fat content is very low and thus the effect of fat soluble drugs is also reduced. Immature blood brain barrier till 8 weeks after birth is also linked to the increased anesthetic effect. Predisposition to hypotension due to poor cardiac compliance.

Geriatrics: The probability or susceptibility of adverse drug reaction is twice in elderly people. The major type of ADR affecting in elderly is Type A i.e. more than 85%. Various reasons justify the statement.

- One reason which can be attributed to this is several health issues affecting at the same time which requires them to take several prescription and over the counter medications, which ultimately enhances the chances of ADR.
- Secondly liver looses ability to metabolize the drugs.
- Water in the body decreases; i.e fat to water content increases. This condition requires the lower dose of drug which dissolves in water since due to less

water it will produce higher concentration in the body, increasing the susceptibility of ADR.

- Kidneys are less able to excrete drugs into urine.

Due to decrease in the efficiency of various body organs and various other facts drugs tend to stay much longer in the body prolonging drugs effect and increase the risk of side effects and adverse drug reactions

Patients with renal and hepatic impairment: Liver and kidney are the major organs for the metabolism and excretion for mostly all the drugs. Impairment of any of these can affect the drug absorption, metabolism, distribution, clearance and ultimately the bioavailability of various drugs. In patients with renal failure, the effect of drugs on the kidneys is lessened because of the loss of the site of action for these drugs. This leads to increasing the dose which in turn leads to more ADRs. One of the important ways is to monitor the laboratory values and adjustments in drug dosage can ultimately prevent an adverse drug reaction using these metabolic and excretory pathways.

ADR Monitoring [7,12]

The first step in identifying ADRs can be performed actively or passively.

Active surveillance: It involves interviewing patients and physicians in a sample of healthcare centres called sentinel sites and also the review of medical history or medical records.. A follow-up questionnaire can be sent to each prescribing physician or the patient at specified intervals to obtain information. In the event of data monitoring, patients may either be identified from electronic prescription data or automated health insurance claims. Another way is to opt registries which are a list of patients presenting similar characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). The potential information can be collected using standardized questionnaires; for example, pregnancy exposure registries for products that are likely to be used during pregnancy.

Another method of ADR monitoring is through clinicians; for example, requesting them for a feedback (for a certain period of time) after the introduction of a new drug in the market or in hospital settings.

Passive Surveillance: The passive methods comprise spontaneous reports and case series of similar reports. A spontaneous report is a voluntary communication by healthcare professionals (doctors, including dentists, nurses and pharmacists) to a industry, regulatory body or an organization (e.g. WHO regional centres, poison control centres) that describes one or more ADRs in a patient who was administered one or more medicinal products. This report is not derived from a study or any organized data-collection scheme. The data accompanying spontaneous reports are often incomplete. But these reports play a major role in the identification of safety signals once a drug is marketed. For instance, temafloxacin, a fluoroquinolone antibiotic, was withdrawn within six months of its introduction because of the association between its use and haemolytic anaemia in otherwise healthy individuals. Spontaneous reporting rapidly identified this ADR because it was rare in the general population and occurred within one week of drug use.

Assessing causality between drugs and suspected reactions [2,3,7,12]

To derive the relationship between a drug and adverse reaction(s), causality assessment is important tool. There is no gold standard for this assessment. Some of the commonly used scales are Naranjo's scale, WHO probability scale, European ABO system, Kramer's scale, Bayesian system, Karch and Lasagna scale, and French imputation method7. The categorization of causal relationships between a drug and the suspected adverse reactions varies with the scale adopted. As per WHO scale the causality relationships are categorized into certain, probable, possible, unassessible/unclassifiable, unlikely, and conditional/unclassifiable, whereas as per Naranjo scale it is categorized as definite, probable, possible or unlikely.

Commonly, the following four aspects should be considered while allocating a clinical adverse event to a drug:

(i) Time related relationship between the suspected reaction and the drug;

(ii) Dechallenge (Termination of drug);

(iii) Rechallenge (reintroduction of drug), and

(iv) Probability of other possible causes.

Reporting adverse drug reactions[12]

The National Pharmacovigilance Programme (NPP) encourages the reporting of all suspected drug-related adverse events, including those suspected to have been caused by herbal, traditional and alternative remedies

Notifying seemingly insignificant or common adverse reactions would be important as it may highlight widespread prescribing problems. The programme particularly solicits reports of:

(i) All adverse events suspected to have been caused by new drugs and 'drugs of current interest'

(ii) All suspected drug interactions and

(iii) Reactions to any other drugs that are suspected of significantly affecting a patient's management, including death, life-threatening conditions (risk of death), hospitalization (initial or prolonged), disability (significant, persistent or permanent) and congenital anomaly. Here intervention is required to prevent permanent impairment or damage.

TIME DURATION TO REPORT SUSAR'S [12]

The specified time duration for reporting of fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) is not later than seven days after the sponsor had information that the case fulfilled the necessary criteria; any follow- up information is to be

provided within a further period of eight days. All other SUSARs are to be notified not later than fifteen days.

REGULATORY AUTORITIES FOR REPORTING OF ADVERSE DRUG REACTIONS [12]

The various ADR regulatory authorities are

1. Committee on Safety of Medicine,
2. Adverse Drug Reactions Advisory Committee,
3. MedWatch and Vaccine Adverse Event Reporting System.
4. The WHO–Uppsala Monitoring Committee (UMC) international database in Sweden maintains all information on ADRs.
5. In India, NPP located at the Central Drugs Standard Control Organization (CDSCO), in New Delhi

Two zonal centres: All India Institute of Medical Sciences, New Delhi for north and east & King Edward Memorial Hospital, Mumbai for south and west

Five regional centres:

1. Department of Pharmacology, JIPMER Pondicherry.
2. TN Medical College, Mumbai.
3. IGMC Nagpur.
4. Lady Harding Medical College, New Delhi.
5. NRS Medical College, Kolkata.

24 peripheral centres: including some medical colleges and hospitals approved by the Medical Council of India, private hospitals, public health programmes and autonomous institutes.

The ADR form is available at any pharmacovigilance centre .The completed form should be sent to the peripheral pharmacovigilance centre or in case of doubts, it can be sent directly to CDSCO. The information provided is handled in strict confidence. The peripheral centre forwards the submitted form to the regional centre where causality analysis is carried out, after which it is sent to the zonal centre. The data are statistically analysed and forwarded to WHO–UMC.

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