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REVIEW ON ADVERSE DRUG REACTIONS: PREDISPOSING FACTORS, MODERN CLASSIFICATIONS AND CAUSALITY ASSESSMENT

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ABSTRACT

Several factors predispose patient to develop adverse drug reactions (ADRs), some of these factors are drug related, patient related, disease related, social and adverse drug related. The contributions of these factors to development of ADRs are very crucial and are well documented in medical literature. It has become necessary for every medical practitioner to consider these factors in order to prescribe the best medication to his patients. The current classification of ADRs is only based on drug known pharmacology and dose dependent of its action. In order to give comprehensive classification, the time course of its appearance and its severity as well as patient susceptibility are taken into consideration. Knowledge of causality assessment enables the medical practitioners to clarify the likelihood that the suspected adverse drug reaction is actually due to the medicine. This requires careful patient monitoring because adverse drug reaction can be difficult and a times impossible to distinguish from patient disease condition. The purpose of this article is to review the factors affecting the development of ADRs, its broader classification and to assess causal relationship between the suspected drug and appearance of ADRs.

KEYWORDS: Adverse drug reactions, adverse drug event, predisposing factors, modern classification, causality assessment and Naranjo probability score.

INTRODUCTION

Modern therapy has improved the way the disease are treated and yielded a lot of success. Despite all the success, ADRs are common often preventable cause of morbidity and mortality.[1] Studies have shown that ADRs are the 4th leading cause of death in USA.[2] Another study revealed that ADRs is one of the major causes of hospital admission, prolonged hospital stays, and additional money spending and time waste on duty as well as poor patient satisfaction.[3] It was also reported that ADRs related hospital admission made up to 10% of all hospitalization.[1] By the time drug is marketed little is known with respect to its safety as only about 1500 people might have been exposed to

the drug during clinical trials. Thus, only ADRs occurring at a frequency greater than 1 in 500 will have been detected before the drug is marketed.[4]

Moreover, the genetic composition of population of people used in the clinical trials cannot represent the population of entire people that will take the drug after it is marketed. A group of scientist proposed that the assessment of ADRs, therefore, is likely to be the most important aspect of drug treatment.[5] This review intended to highlight individual patient factors that may increase the possibility of ADRs, discuss modern classification of ADRs and describe simple approach to the recognition and attribution of causality to the suspected ADRs.

Definition of Adverse Drug Reactions

Adverse Drug Reactions

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'.[6] ADRs unlike adverse drug event, include causal relationship between the drug and its occurrence, it is also differentiated from side effects which may be beneficial.[7]

Adverse Drug Event

Is 'any untoward medical occurrences that may present during the treatment with a medicine but does not necessarily have causal relationship with this treatment'.[8] Adverse drug event refers to any adverse outcome that happened during the treatment but not necessarily caused by the drug itself.[3]

Unexpected Adverse Drug Reaction

Is 'an adverse reaction in which the nature and severity is not consistent with domestic labelling or market authorizations or expected from characterization of the drug'.[7]

Side Effect

Is 'any unintended effect of pharmaceutical product occurring at doses normally used by a patient that is related to pharmacological properties of the drug'.[7] This definition was formulated to include side effects that, although are not the main aim of the therapy, may be beneficial rather than harmful e.g. a β-blocker agent used to treat hypertension may, by β-blockade, also relieve the patient's angina.[7]

Serious Adverse Event

Is 'any untoward medical occurrence that at any dose result in death, or is life-threatening, requires patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or congenital anomaly'.[8]

Medication Error

Is 'any preventable event that may cause inappropriate medication use or patient harm while the medication is under control of health care professional or patient'.[9] It may be related to the professional practice, health care procedures such as prescribing, communication order, product labeling and packaging; also compounding, labeling, dispensing, distribution, administration, monitoring and use of medicine.[10]

Pharmacogenetics and Pharmacogenomics

Pharmacogenetics and Pharmacogenomics is a branch of science which deals with the study of interaction between the therapeutic drug and genetic materials. The two terms can be used inter changeability although there is little difference between them in the initial approach of the science. Pharmacogenetics study an unexpected drug response and try to find a genetic a cause, while pharmacogenomics study genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem.[11]

Predisposing Factors to Adverse Drug Reactions

The risks of developing ADRs are multi-factorial. These factors include drug related factors, patient related factors, disease related factors and social factors.[12]

1. Drug Related Factors

1.1 Drug Dose and Frequency

Dose of medication, frequency of administration and time of the day at which the drug is administered significantly affect the occurrence of ADRs. 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.[12] Aspirin when taken at night yield better anti-platelets action, diuretics like bendrofluazide should not be taken at night to prevent sleep disturbances.[12]

1.2 Poly Pharmacy

It involves prescription of too many medications at same time for a single patient than clinically required.[1] Single patient (especially the elderly) may visit different prescribers for his various disease conditions which may result to poly-pharmacy. Poly-pharmacy may cause ADRs due to the drug additive effect, synergism, duplication, drug interactions, discontinuation of treatment and physiological antagonism.[12] Studies have revealed that possibility of Acute Renal Failure (ARF) in patient treated with poly-pharmacy for less than 30 days in relation to those treated for 31-90, 91-180 and over 181 days had odd ratio of developing ARF of 1.33 ($p < 0.001$), 1.65 ($p < 0.001$) and 1.74 ($p < 0.001$) respectively.[14] Use of non-prescription drugs (OTC and traditional medicine) significantly enhances the occurrence of ADRs. It is reported that patients above 65 years use an average of 2 to 6 prescribed drugs and 1 to 3.4 non-prescribed drugs. In another study it was also stated that patient treated with NSAIDS and corticosteroids at the same time had 15 times risk of developing peptic ulcer than patients not taking either of the two drugs.[15] Prescription cascade may arise when physician could not diagnose ADRs, regarding it as a symptom of disease that warranted an additional medication leading to more ADRs[12] e.g Hyperuricemia caused by thiazide diuretics that lead to prescription of colchicines which in turn may cause diarrhea.[16] It is clinically wrong to use two medicines of same class and efficacy to treat one disease condition because it will promote occurrence of ADR. e.g. use of two therapeutically equivalent NSAIDS or antihistamines.[12]

Strategies to Reduce Medication Errors

The Committee on Quality of Health Care in America (CQHA) has suggested the following measures in order to tackle problems arising from medication errors.[17-18]

1. Standardize prescription writing and prescribing rules.
2. Implement physician order entry.
3. Use pharmaceutical software.

4. Implement unit dosing.
5. Include pharmacist during ward round.
6. Limit varieties of same medicine.
7. Make relevant patient information available at a point of patient care.
8. Educate patient more about his treatment.[9]

2. Patient Related Factors

2.1 Age

Age have significant effect on development of ADRs especially the extreme ages that is paediatric and geriatric patients. 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.[19] However, paediatric patients have low capacity to metabolize drug hence more prone to ADRs.[20] Use of drugs in children pose a lot of challenges in health care delivery, prescribing, dispensing and administration should be done with care.[20] Pediatric medication is calculated based on weight in most of the prescriptions and involves a lot of calculations that are liable to mistakes.[21] Errors due to paediatric dosage calculation have led to ADRs in many instances than in adults due their fragile nature. Elderly patients have low amount of water in the body leading to the increase in fatty tissues relative to water ratio; this causes water soluble drugs to reach higher concentration due to the presence of less water to dissolve them, it also causes decrease in the concentration of fat soluble drugs due to the presence of high fat to dissolve them. Furthermore, ability to excrete drugs via kidney and rate of liver metabolism also decreased in elderly.[22]

2.2 Gender

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.[12] Studies have shown that female patient have more active cytochrome P3A4 hepatic enzymes than male patient indicating the differences in rate of drug metabolism with this enzyme.[23] Hospital studies indicated that women aged 17-44 years visit physician and stays in hospital at twice rate than men.[24] Research conducted in northern India reported that female patients treated with angiotensin converting enzyme inhibitor had higher incidence of cough (37.9%) compared to male patients (15.5%).[25] In another study it was found that women have higher risk of hepatotoxicity than men due to the behavioural, social, physiological and cultural differences.[26] Menstruation, pregnancy and menopause are peculiar to women; their occurrence may significantly affect drug actions.[27]

2.3 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).[28] GIT motility, acidity and tone increase during pregnancy which leads to changes in drug absorption, excretion and metabolism.[28] During pregnancy ADRs may affect only the mother, the feotus or both.[29]

2.4 Foetal Development

Feotus is sensitive to drugs in maternal circulation because of its fragile nature, low metabolism and excretion capacity may cause teratogenicity.[30] Teratogenicity and other ADRs usually occur when drug is taken at first trimester during foetal organ formation.[31] Effect on neonate or infants usually manifest when the drug is taken at the second or third trimester leading to growth retardation, respiratory depression, infection or haemorrhage. These adverse effects depend on the type and amount of drug taken, duration and stage foetal growth.[32]

2.5 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.[33] Decreased in drug clearance in patient with kidney failure is as a result of certain changes that occur in drug transport system and metabolic enzymes. Renal insufficiency also affects non renal drug clearance by introducing another disease or infection that leads to the possibility of ADRs.[12]

2.6 Allergy

Drug independent cross-reactive antigens can triggers sensitizations which can become drug allergy, cross sensitivity usually occur among drugs of same class or of similar structure.[34] After first drug exposure by the patients, second exposure may cause T-cell and antibodies to enter elicitation phase, similar to the type I to IV immune reactions. Drug allergies commonly encountered by patients are type I or type IV reactions while type II and III are very rare.[35] The clinical manifestation of type III reaction include serum sickness (e.g penicillins), lupus erythematosus (e.g quinine), and vasculitis (e.g minocycline).[36] It is believed that Sulponamides and β-lactams antibiotics are common cause of drug allergy.[37]

3. Disease Related Factors

Presence of multiple disease conditions at same time predisposes patient to drug-disease interaction which may eventually lead to ADRs. E.g. increase in the frequency of idiosyncratic toxicity with anti-infective drugs such as trimethoprim-sulphamethoxazole.[38] 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.[39] 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. Drug like prednisolone can cause fluid retention and may worsen congestive heart failure; however, drug-disease interaction may have an insidious onset, thus, monitoring of patient become necessary.[40] Research revealed that AIDS increases the possibility of developing ADRs like Stephen Jonson Syndrome and toxic epidermal necrosis.[41]

4. Social factors

4.1 Race and Ethnicity

Ethnic background is believed to be controlled by genetic factors which are responsible for genetic polymorphism and individual differences in enzyme ability to metabolize drugs, differences in drug receptors and transporters.[42] Occurrence of ADRs differs from one population of patients to another due to genetic differences.[43] In a cohort study to investigate factors that predisposes patient to ADRs by angiotensin converting enzyme (ACE) inhibitors using 2225 people where 19% dropped out due ADRs, it was found that African-American are more susceptible to ACE-related angioedema than other ethnic groups.[3] Research has shown that black people had higher risk of intracranial

hemorrhage and also had 3.0 relative risk of angioedema compared to non-black people. Patient from East-Asia have three times risk of developing cough with ACE inhibitors than white patients.[44] Patients suffering from Parkinson disease who have UDP-glucuronosyl-transferase 1A9 genotype are more susceptible to ADRs when treated with catechol-O-methyltransferase inhibitors.[45] Current research indicated that patient that developed ADRs have higher CYP1A2, low allele combinations (8/12; 67%) and lower CYP1A2-mRNA than patient that do not developed ADRs (6/22; 27%, p = 0.019).[46]

4.2 Alcohol

Alcohol affect drug metabolism and promote development of ADRs.[47] 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.[48] Similarly, chronic alcohol intake activates enzymes which accelerate drug metabolism and causes toxicity.[12] Taking alcohol with NSAIDs by patient having peptic ulcer or gastritis may cause internal hemorrhage.[49] Concurrent ingestion of alcohol with some drugs has led to many ADRs like nausea, vomiting, headache, drowsiness, fainting, and hypotension.[50]

4.3 Smoking

Smoking is identified as one of the risk factor for peptic ulcer, cardiovascular diseases and cancer.[51] 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.[52] 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.[53] 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.[54]

Modern Classification of Adverse Drug Reaction

Generally, ADRs are classified as type A (Dose-related or Augmented), type B (Non-dose related or Bizarre), type C (Dose-related and Time-related or Chronic), type D (Time-related or Delayed), type E (Withdrawal or End of use), type F (Unexpected or Failure of therapy.[7] In order to improve ADRs management, new system of classification based on drug dose, time course and patient susceptibility to ADRs is proposed.

Dose Relatedness

Traditionally, immunological and other ADRs have been considered not to be dose related. Actions of drugs whether beneficial or harmful depend mainly on the dose administered. Example of immunological reactions that are clearly dose dependent reactions are e.g. hay fever in response to high pollen counts[55]; immunological response to hepatitis B vaccine[56]; desensitization by increasing the dose of antigen e.g. cephalosporins[57]; and type IV hypersensitivity skin reactions.[58] It is generally wrong to consider type B ADR as non-dose dependent.[59] Therefore, it is more appropriate to divide ADRs into those that occur at supra-therapeutic doses (toxic effect) and those that occur at standard therapeutic effect (Collateral effects).[60]

Time Relatedness

The pharmacological action of drug depends on its concentration at the receptor site and time course to reach the receptor site.[60] Based on the time course, adverse drug reaction can be divided into time dependent and time independent reactions.[60]

Time Dependent Reactions

Time defendant reactions are divided into six sub-groups:

i. Rapid Reaction

It is caused by rapid administration of drug parenterally, e.g. the red man syndrome with vancomycin.[61]

ii. First Dose Reaction

This type of reaction occur when the first dose is administered and not necessarily after a long duration e.g. hypotension that occurred after the first dose of angiotensin converting enzyme inhibitor (ACEIs) and type 1 hypersensitivity reaction, e.g. development of anaphylaxis to penicillin at first exposure.[62]

iii. Early Reaction

At the beginning of the treatment patient may experience some reaction which become tolerated with time (E.g. nitrate induced headache).[60]

iv. Intermediate Reaction

Intermediate reaction does not occur immediately, it takes some times before it happens. However, after some days if the patient does not experience any reaction, there is high possibility that the reaction may not happen at all. Hypersensitivity reaction type II (e.g. thrombocytopenia to quinines), type III (e.g. interstitial nephritis to penicillin) and type IV (e.g cutaneous hypersensitivity to antihistamines) and the penicillin pseudo-allergic rash are examples of intermediate reactions. Other intermediate reactions are non-allergic e.g. increase risk of neutropenia with carbimazole and venous thrombosis with antipsychotic drugs.[60]

v. Late Reaction

This occurs rarely or not at all at the beginning of treatment. Usually, late reaction appears after repeated administration of the drug e.g. tardive dyskinesia with dopamine receptor antagonist.[60] Late reaction also includes reaction after withdrawal or dose reduction e.g. myocardial infarction (MI) after withdrawal of β-blocker and hypotension after withdrawal of methyldopa.[60]

vi. Delayed Reaction

Happens long-time after the completion of treatment e.g. teratogenesis (e.g. phocomelia due to thalidomide) and vaginal adenocarcinoma in women treated with diethylstilbestrol.[60]

Time Dependent Reactions

Time dependent reaction occurs at any time during the exposure and does not depend on the time course e.g. digoxin toxicity in association with potassium depletion and digoxin toxicity due to poor renal function.[60]

Susceptibility Relatedness

Under this section ADRs are categorized in relation to patient susceptibility in a given population.[60] The risk of developing ADRs differs from one patient to another. Several factors discussed earlier in this article predispose patient to develop ADRs, the type and nature of ADRs depends on patient factors that made him vulnerable. Factors affecting the development of ADRs include patient related, social factors, drug related, disease related and ADRs related factors.

Causality Assessment

It is essential in every clinical setting for a medical practitioner to carry out broader diagnosis of patient. This involves not only diagnosing the patient based on the disease he presented with but also possibility of ADRs being the chief complaint or its occurrence in a near future when the treatment is initiated.[7] Sometimes it may become necessary to establish base line parameters at the beginning of treatment in anticipation of ADRs, this includes laboratory investigations such as plasma concentration, allergy test and biopsy as well as base line organ functions (e.g. Kidney, Liver and thyroid function). The whole idea is to provide means of assessing the real outcome of the treatment as drug may alter some of the parameters.[7]

Assessment of ADRs may be difficult to establish based on clinical diagnosis because some ADRs tend to mimic natural disease occurring process.[1] Although some ADRs (e.g. extrapyramidal disorder) are peculiar to some class of drugs, it is necessary for a clinician to establish the following: 1. time relation between the use of drug and appearance of ADRs, 2. differential diagnosis to evaluate other possible causes, 3. selection of the culprit drug based on the pattern of the reaction, 4. exclusion, de-challenge or re-challenge.[7] Before one can assess ADRs with high level of precision, several factors that predisposes patient to ADRs should be taken into consideration. A part from the drug itself, certain changes in pharmacokinetic or pharmacodynamic profile of the drug by disease condition, body physiology, life style, and concurrent therapy may influence the occurrence of ADRs.[12] There is need for a clinician to interview the patient and establish drug history for him to be able to relate the patient present condition with previous prescription, non-prescription or traditional medicine consumed by the patient.[1]

It is important to note that appearance of ADRs in patient while taking several medications does not guaranteed that one of the drugs is the cause, also lack of relationship between the appearance of ADRs and time within which the drug was administered does not ruled out the drug as a possible cause.[1] It is unwise to treat unrecognized drug related ADRs with another drug as it may predisposes the patient to injury and poly pharmacy.[63] The main purpose of causality assessment is to find out the level of probability or how certain one can be that the suspected ADRs is actually due to the drug. Several scales were used to assess causality e.g. WHO scale, Hart wig scale, European ABO system and Naranjo scale; Naranjo Algorism is the most simple and widely used method of ADRs assessment, it categorizes ADRs into: 1. Certain 2. Probable 3. Possible 4. Unlikely and 5. Doubtful.[64] The Naranjo Algorism have assigned scores to each category; Naranjo probability scale with score 9 = Definite/Certain, 5-8 = Probable, 1-4 = Possible and score 0 = Doubtful.[64]

Table 1: Naranjo Probability Scale.[1]

S. No.		Yes	No	Don't know
1	Was there any conclusive report on this reaction before?	+1	0	0
2	Did the reaction occur after the ingestion of the suspected drug?	+2	-1	0
3	Was there any relief after withdrawal of the suspected drug or when antagonist is administered?	+1	0	0
4	Did the reaction reoccur after re-challenge with same drug?	+2	-1	0
5	Was there any possible cause of this reaction apart from the suspected drug?	-1	+2	0
6	Did the reaction reoccur when placebo was administered?	-1	+1	0
7	Did the suspected drug accumulate in toxic concentration in any of the body fluid?	+1	0	0
8	Did the reaction increase when the dose of the drug added or decrease when the dose is reduced?	+1	0	0
9	Based on history, did the patient react to same drug or similar drug before?	+1	0	0
10	Was the suspected ADR confirmed by any established facts?	+1	0	0

SCORE 9 = definite; 5-8 = probable; 1-4 = possible; 0 = doubtful.

CONCLUSION

All health care providers need to embrace the approach of Evidence Based Medicine (EBM) which is the most conscientious, explicit and judicious use of current best evidence in making decision about the care of individual patients. Majority of treatments are not emergency, this gives the medical practitioners chance to make broader diagnosis of patient by asking patient many questions and by going through medical history. It is important to consider all the possible factors that may contribute to drug hazards to enable the medical practitioner to prescribe the best possible medication to his patients. Adequate knowledge of adverse drug reaction by doctors, pharmacist and nurses will improve the standard of health care delivery services and post-marketing safety studies. It is imperative for all the health care providers to consider the possibility of ADRs as a chief complain when the patient is presented to the hospital or possibility of its occurrence when the treatment is initiated. Sometimes it may become necessary to establish base line organ function and other laboratory parameters at the beginning of the treatment in order to be able to assess the real outcome of the treatment as drugs may alter these parameters.

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