

## REVIEW ARTICLE

## ADVERSE DRUG REACTIONS (ADRS): FACTORS AND ROLE OF PHARMACIST IN THEIR PREVENTION

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Adverse drug reactions (ADRs) are the undesirable effects of drugs even when administered in daily normal doses. It has been seen that ADRs may arise even after single administration of drug(s), however, long term therapies are more prone to ADRs. Currently it has become a burning issue all around the world and connected with financial expansion owing to hospitalization. Pharmacists are the custodians of drugs especially clinical pharmacists play a vital role in preventing the risks of ADRs. This review deals with the factors leading to possible ADRs, its prevention and the role of pharmacist in management of ADRs.

**Keywords:** Adverse drug reaction, ADRs, Factors of ADRs, prevention, management, pharmacist, pharmacy

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## INTRODUCTION

Medicines have been known to elicit a desired therapeutic outcome and also have the likelihood of causing undesirable adverse effects. According to the World Health Organization (WHO) and definitions by Karch and Lasagna, an adverse drug reaction (ADR) is "any reaction to a drug that is noxious and unintended, and occurs at doses used for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended response".<sup>1</sup> As of late the term adverse drug event (ADE) is opted which includes medication errors. In comparison to AIDS, pulmonary disease, motor car death and accidents, ADRs are alleged to be the 4<sup>th</sup> leading cause of death.<sup>2</sup> The meaning of ADR distinguished from side effects, as side effects may be beneficial as well. In 10-20% of hospitalized patients, there is no less than one ADR to turn up.<sup>3,4</sup> Post marketing surveillance or pharmacovigilance or monitoring ADR, initiated in the 1960s by the WHO after 'thalidomide' crisis, is undertaken by more than 70 countries throughout the world for early detection and prevention of ADR. Traditional and herbal remedies may also lead to particular ADRs when either used on their own or in combination with other medications.<sup>4,5</sup> The significance of ADR in causing mortality and morbidity also results in an increase in the cost of health care.<sup>6-8</sup> Therefore pharmacists along with other health care professionals need to work as a team in the detection, management, prevention and reporting of ADRs leading to the wellbeing of the patient safety and a decrease in healthcare cost.

## EPIDEMIOLOGY

ADRs are a major cause of morbidity and mortality worldwide and 5.3% ADRs are associated with hospital admission and affects 2.2 million people

causing a hundred thousand deaths per year.<sup>9</sup> Cost associated with ADRs is 136 \$billion yearly. ADRs for ambulatory patients are unknown and nursing home patients ADRs rate are 350,000 yearly.<sup>7,10,11</sup>

## CLASSIFICATION

ADRs may be classified as:

**Type-A (Augmented) reactions:**

These are pharmacologically based reactions that have a quantitative distinction in response, are dose related, distinctive, and unwanted, quite wide spread and expected. They comprise of toxic and side effects as well as an outcome of drug withdrawal. These are usually undesirable for patients. Example includes bruising by warfarin and heparin.

**Type-B (Bizarre) reactions:**

These are based on the distinctive features of patients that have a qualitative variation in response to a drug, not usually related to dose and infrequent, often bizarre, erratic in nature and often serious.<sup>12</sup> These are often not known until the drugs have been marketed. These reactions are also thought to be related to environmental and genetic factors.<sup>13</sup> Example includes penicillin related anaphylactic reaction.

**Type-C (Chronic) reactions:**

These are the reactions that occur with long-term use of medicines for example Benzodiazepine dependence and analgesic nephropathy. They are identifiable and can be foreseen.<sup>14</sup>

**Type-D (Delayed) reactions:**

It is due to extended exposure (carcinogenesis) or limited exposure at a crucial time (teratogenesis).

**Type-E (Ending of Use) reactions:**

It occurs when there is a sudden ceasing of chronic therapy, e.g. of adrenal steroid causing rebound

adrenocortical insufficiency, of opioid causing the withdrawal syndrome.<sup>15</sup>

Approximately 80% of all ADRs are type-A in nature.<sup>16</sup> Most of the drugs prescribed exhibiting type-A reaction are reported in handbooks and drug literature leaflets.

#### **Factors affecting Incidence of ADRs:**

There are certain factors responsible to increase the risks of ADRs. They are discussed below;

#### **Age of Patient:**

It is estimated that possible ADRs are also dependent on age of the patient. Geriatric patients take more medicines than patients of other age groups due to co-morbidities and complexity of medical problems. ADRs may result due to drug-drug interaction (owing to poly therapy), the modification of metabolic enzymes. Elder patients are more prone to Type-A reactions than Type-B.<sup>17-19</sup> Similar is the case with children, the incidence of ADRs is more in paediatrics age group than adults. There are several reasons like metabolic enzymes are not fully developed in infants and children, so the accumulation of drug is a promoting factor for the development of ADRs.<sup>20</sup> In addition the body fats are low, creating problematic situation for lipid soluble drugs.<sup>21</sup> Another reason is the unavailability of the scientific investigations on such small age group.<sup>22</sup>

#### **Gender of Patient:**

It is a well-known fact that males and females are physiologically as well as anatomically different from one another. It has been reported time to time that females are more susceptible to develop ADRs than males. The frequency of ADRs reported by women are twice as compared to men.<sup>23,24</sup> Pharmacodynamics differences are also exist in males and females. Chlorpromazine, an anti-psychotic drug is more effective in females than males.<sup>25</sup>

Serious ADRs have been frequently reported in females including neuropsychiatric and cardiovascular effects. The common classes of drugs for reporting gender based ADRs are genito-urinary, sex hormone, antineoplastic, anti-parasitic and respiratory.<sup>26</sup>

#### **Genetic Factors:**

Individuals having abnormal or altered drug metabolism are more susceptible to ADRs. Genetic polymorphism and other cellular mechanisms are involved in irregular drug metabolism. It is documented that globally about 200 million people are G6PD (glucose-6-phosphate dehydrogenase) deficient. Such individuals are prone to haemolytic anaemia especially after ingestion of some anti-malarial drugs and sulphonamides.<sup>27</sup> Additionally,

genetic polymorphism also have been seen in different other metabolic enzymes like cytochrome P450, leading to rapid or slow metabolism of drugs. These transformations result in the development of different ethnic groups having distinct phenotypes.<sup>28</sup> Morphine is administered in the form of codeine as pro-drug. Accumulation of pro-drug and poor therapeutic response are the predicted consequences due to mal-functioning of CYP P450.<sup>28</sup> The accumulation of drug inside the body<sup>28</sup> and the changes in drug target due to genetic variation are considered as a prime reason to develop ADRs.<sup>27</sup>

#### **Renal Function:**

The percent creatinine clearance illustrates the function of kidney. In renally compromised patients (poor kidney function) it results in accumulation of drugs being metabolized by kidney. It is also reported that alteration of kidney function affects the plasma protein binding as well as drug metabolism through liver. Reduced clearance finally causes deposition of drug for longer time and hence results in possible ADRs.<sup>29</sup> Doses of drugs must be adjusted accordingly and drug monitoring is considered to be a prime requirement in such patients.

#### **Polypharmacy:**

Monopharmacy has been replaced with polypharmacy globally. Polypharmacy is a need for some critically ill patients especially in geriatrics. It has been noticed that hypertension is comorbid with diabetes mellitus and peptic ulcer. In such case a patient may receive different regimens to stabilize the mentioned complaints. The possible reasons for ADRs are drug-drug interaction, synergistic effect of drugs, additive effects, and physiological antagonisms etc.<sup>20</sup> Antiviral regimen is complex in nature and contains protease inhibitor (PI), extensively metabolized by Cytochrome P450. All those drugs responsible to decrease the activity of Cytochrome P450, would definitely result in increased accumulation of PIs. Similarly drugs responsible to induce cytochrome P450 will result in decreased plasma concentration of drugs.<sup>30</sup>

#### **Multiple Disease State:**

The intensity as well as frequency of reporting ADRs is dependent on nature and the status of illness. Drug metabolism becomes a big question mark in patients with renal insufficiency and liver dysfunctions. Both result in reduced metabolism of many drugs and their associated ADRs. It is basically drug-disease interaction. For example some drugs have the ability to cause sodium retention, in turn increase the blood pressure of hypertensive patients and may result in serious ADRs. Other examples include worsening of asthma

due to use of aspirin and beta adrenoceptor blockers, aggravation of thrombo-embolic disorders due to intake of oral contraceptives and many others.<sup>31</sup> Even deaths have been reported in cardiac patients due to cyclo-oxygenase users.<sup>32</sup>

#### **Social Factors:**

The incidence of ADRs is also dependent upon alcohol consumption and smoking since both interfere with metabolism of different drugs. Alcohol consumption and smoking are aggravating factors for the development of ulcers especially peptic ulcers.<sup>33,34</sup> The high intake of alcohol and tobacco are also associated with common complaints of dry mouth or xerostomia.<sup>35</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) must be carefully administered in smokers and drinkers since NSAIDs commonly induce gastric and peptic bleedings.<sup>36</sup> Smoking increases the metabolism of drugs by liver, resulting in reduction of therapeutic effects of drugs. Alcohol drinking and smoking should also be avoided especially in drugs of narrow therapeutic index.

#### **MANAGEMENT OF ADRs**

Studies have shown that lots of adverse effects can be preventable and detected through the intervention system.<sup>37,38</sup> Sufferers of ADRs need to be examined to avoid ADRs.<sup>9,10,39,40</sup> Like the patients' age evaluation because decline organ function is seen in elder patients with decreased hepatic or renal clearance. These factors are supposed to be predisposing aspects leading to ADRs. Likewise, neonates may have the same problem. Patient with human immunodeficiency virus (HIV), having greater risk of ADRs compared to general population.<sup>37</sup>

Few others factors like intravenous injection also have a potential for causing ADRs. Immediate release product has also been associated with causing some ADRs that do not usually appear with sustained release products. Most important factors are multiple prescriptions and self-medication.<sup>9</sup> If the adverse drug reaction is non-immune: side effects, secondary effects, toxicity, drug interaction, drug idiosyncrasy, drug intolerance, and pseudo allergic reaction. Then for the management of ADRs we can do the following: changing the dose of drug, replacement with alternate medicine, use of prophylactic regimen and patient and physician education is also important for the reduction of ADRs. Desensitization of IgE antibody as a prophylactic regimen in future may be prudent; if re-administration of drug is contraindicated then it must be stopped.<sup>41</sup> ADRs can be prevented by use of technology. Many healthcare systems have implemented new technologies to

minimize the medication error and drug interaction.<sup>10,42-44</sup> Medications errors were potentially reduced by using drug interaction screening software and computerized medical records and educating the physician and pharmacist for potentially serious ADRs.<sup>45</sup> The healthcare providers like physicians and pharmacists must address the ADRs. Pharmacists play a significant role in recognizing, monitoring, evaluating documenting and communicating ADRs.<sup>46,47</sup> Pharmacists are extensively educated in the area of pharmacology therapeutics and pharmacokinetics and are easily accessible to the patient, therefore, can avert occurrence of any lethal situation.

#### **Role of Pharmacist in the Management of ADRs:**

As seen through various studies and the basic concept of pharmaceutical care, a pharmacist plays a pivotal role in the identification, detection, prevention, and management of drug-drug interactions, drug-food interactions and ADRs. Pharmacist can carry out such activities in inpatient setting, while taking part in viewing charts during ward rounds, and during medication management while dealing with prescriptions. Since pharmacists have a vast knowledge on drugs and therapeutics, their ability to discover and deal with ADRs is quite important.<sup>4</sup>

Keeping in view the reporting of ADRs, according to a study carried out by Sriram *et al* on the prevalence of ADRs, a pharmacist's participation enhances reporting rate with higher calibre. The intervention of pharmacists by organising lectures and group discussions thus providing information about the importance, seriousness, preventability and necessity of reporting shows heightened improvement of knowledge, attitude and perception about ADRs.<sup>48</sup> All health professionals play their respective roles in balancing between benefits and risks of medication when it is introduced in the market. However, the expertise of a pharmacist about a drug, especially if newly marketed, play a more important role in ADRs reporting to the authorities which helps in either withdrawing the product from the market or cause labelling changes.<sup>8</sup>

Pharmacists working in community pharmacy have an added advantage of detecting and reporting ADRs while dealing with on the counter prescriptions and herbal products.<sup>49</sup> In a community pharmacy, a pharmacist may not have direct and definite patient list but the patients coming to the same pharmacy to refill their prescription gives the pharmacist an opportunity to detect a possible ADR that the patient might be experiencing and can help in the management and the reporting of the said ADR.<sup>50</sup>

## CONCLUSION

Patients' safety is now becoming a global concern. The prime requirement of time is to control the ADRs, to avoid health and economic crises. Responses of drugs should need to be re-evaluated and thorough drug monitoring is required especially in prolong treatment to lessen the risks of ADRs. Clinical pharmacists must work together with physicians to aid reporting of ADRs both in hospital and community settings.

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