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REVIEW

Factors affecting the development of adverse drug reactions (Review article)

Muaed Jamal Alomar *

Al Ain University of Science and Technology, Al Ain, United Arab Emirates
Faculty of Pharmacy and Health Sciences, Clinical Pharmacy Department, United Arab Emirates

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KEYWORDS

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Abstract *Objectives:* To discuss the effect of certain factors on the occurrence of Adverse Drug Reactions (ADRs).

Data Sources: A systematic review of the literature in the period between 1991 and 2012 was made based on PubMed, the Cochrane database of systematic reviews, EMBASE and IDIS. Key words used were: medication error, adverse drug reaction, iatrogenic disease factors, ambulatory care, primary health care, side effects and treatment hazards.

Summary: Many factors play a crucial role in the occurrence of ADRs, some of these are patient related, drug related or socially related factors. Age for instance has a very critical impact on the occurrence of ADRs, both very young and very old patients are more vulnerable to these reactions than other age groups. Alcohol intake also has a crucial impact on ADRs. Other factors are gender, race, pregnancy, breast feeding, kidney problems, liver function, drug dose and frequency and many other factors. The effect of these factors on ADRs is well documented in the medical literature. Taking these factors into consideration during medical evaluation enables medical practitioners to choose the best drug regimen.

Conclusion: Many factors affect the occurrence of ADRs. Some of these factors can be changed like smoking or alcohol intake others cannot be changed like age, presence of other diseases or genetic factors. Understanding the different effects of these factors on ADRs enables healthcare professionals to choose the most appropriate medication for that particular patient. It also helps the healthcare professionals to give the best advice to patients. Pharmacogenomics is the most recent science which emphasizes the genetic predisposition of ADRs. This innovative science provides a new perspective in dealing with the decision making process of drug selection.

* Address: P.O. Box 222319, Al Ain, United Arab Emirates. Tel.: +971 507157641; fax: +971 37378728.
E-mail address: muayyad74@yahoo.com.

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Contents

1. Introduction

Safety issues arise whenever medical choices have to be made (Bauer, 2008). ADRs can occur in all settings where healthcare is provided. Most of the current evidence comes from hospitals because the risks associated with hospital treatment are higher (Yurdaguel et al., 2008). Many such events occur in other healthcare settings such as consulting rooms, nursing homes, pharmacies, community clinics and patients' homes (Steven et al., 2008). While the drug manufacturing process has been revolutionized by modern techniques, drug safety assessment stays behind and is still reliant on technologies that have been used for several decades (Powley et al., 2009). Current conceptual thinking on the safety of patients places the prime responsibility for ADRs on deficiencies in system design, organization and operation – rather than on individual practitioners or products. Berwick and Leape (1999) recommended that checks and quality assurance should be built into the use system, rather than assuming that all will be well. By the time a drug is marketed, only about 1500 patients may have been exposed to the drug. Thus, only those ADRs occurring at a frequency of greater than 1 in 500 will have been identified at the time of licensing (Andrade et al., 2007). Pirmohamed et al., 1998 suggested that the assessment of ADRs therefore is likely to represent an important aspect of drug therapy. Bates et al., 2003 showed that the overall rate of ADRs is estimated to be 6.5 per 100 admissions; 28% of these reactions are preventable. Once marketed, a drug loses the scientific environment of clinical trials and is legally set free for consumption by the public (Russell et al., 1992). At this point, most drugs will only have been tested for short-term safety on a limited number of previously defined and selected individuals.

ADR is defined as a response to a drug 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 (WHO, 1973). It is also defined as an undesirable effect, reasonably associated with the use of the drug that may occur as a part of the pharmacological action of a drug or may be unpredictable in its occurrence (Edwards and Aronson, 2000).

1.1. Magnitude of ADRs

ADRs are one of the leading causes of morbidity and mortality in healthcare. The Institute of Medicine, in the United States (US) (2000) reported that between 44,000 and 98,000 deaths occur annually from medical errors. Of this total, an estimated 7000 deaths occur due to ADRs. Analyzing 39 studies of the American pharmaceutical system over four decades found that in 1994, 106,000 people died as a result of ADRs. More than 2 million suffered serious side effects (Pomeranz and Bruce, 1998). These figures showed that there was a trend of increasing death and injury from ADRs. That would make ADRs the fourth leading cause of death in the US behind heart disease, cancer and strokes (Jemal et al., 2005). In another survey conducted by the American Society of Health-System Pharmacists, Byrne et al. (2006) found that 85% of patients who responded to the survey expressed concerns about at least one drug-related issue, such as receiving interacting drugs, having harmful adverse effects from a drug, or receiving the wrong drug. ADRs are a significant public health problem in the world. Not only do ADRs cause death and injury but they also affect the length of stay in hospitals which in turn leads to increased healthcare costs and decreased patient productivity. Moura et al. (2009) determined the frequency of ADRs in intensive care units and evaluated their effect on the length of stay and found out that each ADR presented by the patient was related to an increase of 2.38 days in the ICU. In research

done at the University of Liverpool, 18,820 patients were assessed. It was found that, a total of 1225 admissions were related to an ADR, giving a prevalence of 6.5%. The average stay was 8 days, which accounted for 4% of the hospital bed capacity (Nainggolan, 2004). Another prospective cohort study was carried out to evaluate more than 1200 outpatient prescriptions, survey patients, and conduct a chart review during a 4-week period. The researchers discovered that 25% of patients experienced an ADR with selective serotonin-reuptake inhibitors, beta blockers, angiotensin-converting-enzyme inhibitors, and nonsteroidal anti-inflammatory drug classes being the most frequently implicated. The rate of ADRs has approached 27 per 100 patients (Gandhi et al., 2005). ADR reporting has yet to be developed adequately. The need for increased awareness of the importance of ADR reporting is vital in Malaysia (Aziz et al., 2007).

1.2. Data sources

A systematic review of the literature between the period of 1991–2012 was made based on PubMed, the Cochrane database of systematic reviews, EMBASE and IDIS. The articles searched for included original articles, WHO and FDA reports and institute of medicine reports. Keywords used are: medication error, adverse drug reaction, iatrogenic disease, factors, ambulatory care, primary healthcare, side effects, and treatment hazards. Search is done regardless of the date of publications.

1.3. Factors affecting the occurrence of ADRs

Kitteringham et al. (1994) suggested that for most adverse reactions, particularly the idiosyncratic drug reactions, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infection or the use of other drugs for different diseases. The majority of ADRs occur as a result of the extension of the desired pharmacologic effects of a drug, often due to the substantial variability in the pharmacokinetics and pharmacodynamics seen among patients. Pharmacological, immunological, and genetic factors are involved in the pathogenesis of ADRs. Factors that predispose to pharmacological ADRs include dose, drug formulation, pharmacokinetic or pharmacodynamic abnormalities, and drug interactions. The metabolic conversion of drugs to metabolite is now established as a requirement for many idiosyncratic drug reactions (Masubuchi et al., 2007). Increased levels of reactive drug metabolites, their impaired detoxification, or decreased cellular defense against reactive drug products appears to be an important initiating factor (Guengerich and MacDonald, 2007). Immunological and genetic factors may play a role in the reaction of the body toward the drugs given. Torpet et al. (2004) suggested ethnic variations also play an important role in the development of ADRs. Evans (2005) found that some risk factors are consistent for all ADRs and across multiple therapeutic classes of drugs, while others are class specific. High-risk agents should be closely monitored based on patient characteristics (gender, age, weight, creatinine clearance, and number of comorbidities) and drug administration (dosage, administration route, number of concomitant drugs). Factors which might increase the possibility of the occurrence of ADRs include; extremes of age, gender, multiple drugs, disease state, past history of ADR or allergy, genetic factors, large doses and many other factors. Discontinuation of the drugs or changing doses may be an important factor in developing ADRs to certain drugs in certain populations especially the elderly. Agency for Healthcare Research (2001) suggested another potential cause of ADRs can stem from the clinician's reluctance to treat with adequate doses of a drug for fear of causing drug toxicity. ADRs may be caused by errors in manufacturing, supplying, prescribing, giving, or taking drugs. Eighteen percent of drugs related to ADRs in the Harvard medical practice study were judged to be due to negligence, defined as failure to meet the standard of care reasonably expected of a physician qualified to take care of the patient in question (Leape et al., 1991). Bates et al. (2003) suggested ADRs occurred frequently in the peridischarge period, and many could potentially have been prevented or ameliorated with simple strategies. Factors affecting the occurrence of ADRs are subdivided into five groups; Patient related factors, Social factors, Drug related factors, Disease related factors and ADR related factors.

2. Patient related factors

2.1. Age

All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. Age is a very important factor which affects the occurrence of ADRs. Elderly patients with multiple medical problems who are taking multiple drugs, those who have a history of ADRs, and those with a reduced capacity to eliminate drugs are at high risk for ADRs. A study by Debellis et al. (2003) about the incidence and preventability of ADRs among older persons in the ambulatory setting concluded that ADRs are common and often preventable among older persons in the ambulatory clinical setting. More serious ADRs are more likely to be preventable. Prevention strategies should target the prescribing and monitoring stages of pharmaceutical care. Interventions focused on improving patient adherence with prescribed regimens and monitoring of prescribed drugs. Elderly and pediatric patients are particularly vulnerable to ADRs because drugs are less likely to be studied extensively in these extremes of age, and drug absorption and metabolism are more variable and less predictable in both of these groups. Efforts are needed to predict and prevent the occurrence of ADRs in children (Bates et al., 2001). Infants and very young children are at high risk of ADRs because their capacity to metabolize the drug is not fully evaluated. The following are some factors that might affect the development of ADRs in neonates (Clavenna and Bonati, 2008):

1. Neonates have immature renal tubular function when they are below the age of 8 weeks, avoiding digoxin, aminoglycosides, ACE inhibitors, NSAIDs is a must (De-gregori et al., 2009).
2. Physiologic hypoalbuminemia in neonates affects drug dosing. Caution is recommended when dealing with high protein binding drugs such as NSAIDs (Anderson and Lynn, 2009).
3. Neonates, have low body fat; they might be affected by fat soluble drugs (Ibáñez et al., 2009).
4. Increased anesthetic effects due to immature blood brain barrier at < 8 weeks of age (Schoderboeck et al., 2009).

5. Predisposition to hypotension due to poor cardiac compliance and immature baroreceptors (Pellicer et al., 2009).

Older people are at high risk of developing an ADR for several reasons. They are likely to have many health problems and thus take several prescriptions and over the counter drugs. As people get older, the liver loses the ability to metabolize drugs (Budnitz et al., 2007). Also, older people are more than twice as susceptible to ADRs as younger people (Hajar, 2003). As people age, the amount of water in the body decreases and the amount of fat tissue relative to water, increases. Thus, in older people, drugs that dissolve in water reach higher concentrations because there is less water to dilute them, and drugs that dissolve in fat accumulate more because there is relatively more fat tissue to store them. Also, as people age, the kidneys are less able to excrete drugs into the urine, and the liver is less able to metabolize many drugs. Jimmy and Padma (2006) in their study concluded that the incidence of ADRs among elderly adults and older adults was significantly higher than other age groups. They also elaborated that the type of ADR is different among age groups, type A reactions were more common among elderly adults (85.9%) and type B reactions were more common in adults (35%) compared to other age groups. Because of all age-related changes, many drugs tend to stay in an older person's body much longer than they would in a younger person's body, prolonging the drug's effect and increasing the risk of side effects (Klotz, 2009).

2.2. Gender

The biological differences of males and females affect the action of many drugs. The anatomical and physiological differences are body weight, body composition, gastrointestinal tract factors, liver metabolism, and renal function. Women in comparison to men have lower bodyweight and organ size, more body fat, different gastric motility and lower glomerular filtration rate. These differences can affect the way the body deals with drugs by altering the pharmacokinetics and pharmacodynamics of the drugs including drug absorption, distribution, metabolism and elimination. Gender plays a role in the effect on ADRs. A study of sex differences in ADRs to antiretroviral drugs indicates potential sex differences in the frequency and severity of ADRs to antiretroviral drugs (Ofotokun and Pomeroy, 2003). Hepatic enzyme CYP3A4 is more active in females than males which lead to different effects on drug metabolism (El-Eraky and Thomas, 2003). They also suggested that women are more prone than men to develop torsade de pointes ventricular tachycardia during the administration of drugs that prolong cardiac repolarization. Women restrict their activity because of acute and chronic health problems approximately 25% more days per year than do men, spending approximately 40% more days in bed each year than men (Legato, 1998). Women aged 17–44 years have twice as many physician visits and hospital stays as men. When reproductive and other sex-specific conditions are excluded, the difference in hospital stay virtually disappears, but the difference in ambulatory care is still approximately 30%. After the age of 45, when all sex-specific conditions are excluded, women continue to have approximately 10–20% more physician visits, with men having a greater frequency of hospitalization (Ensom, 2000).

In a north Indian study by Singh et al. (1998) on angiotensin converting enzyme inhibitors and cough, females had a higher incidence of cough compared to males (37.9% vs. 15.5%). In Chinese populations, the metabolism of midazolam in women is more than in men due to the activity of CYP3A4 (Labbé et al., 2000). Moreover, the pharmacodynamic differences between men and women are particularly seen with cardiac and psychotropic drugs. Chlorpromazine and fluspirilene seem to be more effective in women than in men for the same dosage and plasma concentration (Bing et al., 2003). Some drugs affect one sex without the other, e.g. colchicine which is used for the treatment of many diseases including Familial Mediterranean fever might affect fertility in males but not in females (Sternberg and Hubley, 2004). On the other hand, hepatic drug reactions are more common in females. It was estimated that the female gender is a risk factor for hepatotoxicity more than men (Rajani et al., 2004). Gender differences refer not only to biologic differences but to physiologic, social, behavioral, and cultural differences as well. Results of various animal studies illustrated the fact that a significant difference in drug metabolism and elimination due to gender difference provide an impetus for sex based research in humans (Meyer et al., 2009). Recent advances in the characterization of specific isoenzymes of drug metabolism paved the way for preliminary identification of the enzyme system affected by sex. Limited current studies showed apparent CYT P450 (CYP 3A4) activity higher in females than in males while other enzymes are increased in males (Waxman and Holloway, 2009). Men and woman show different pharmacodynamic responses to various drugs which may lead to different therapeutic responses. Female specific issues such as pregnancy, menopause and menstruation may have profound drug effects in humans (Mitchell et al., 2009). A few clinically significant ones like increased elimination of anti-epileptics decreasing their efficacy in pregnancy, oral contraceptives interfering with metabolism of many drugs and conversely certain drugs can impair contraceptive efficacy (Dorothy et al., 2008). Moreover, the most pronounced differences between women and men (54% vs. 46%, respectively) were seen in a study about the incidence of ADRs caused by cardiovascular medications; low-ceiling diuretics caused a relative risk of 4.02, cardiotonic glycosides caused a relative risk of 2.38, high-ceiling diuretics caused a relative risk of 2.10 and coronary vasodilators caused a relative risk of 0.77 (Rodenburg et al., 2012).

One of the most consistent observations in health research is that women report symptoms of physical illness at higher rates than men. Still unresolved is whether this is due to clinical differences in morbidity or disease severity, or to differences in the following: illness behavior – women are more likely than men to interpret discomfort as symptoms; symptom perception – women's attentiveness to body discomfort increases their perception of symptoms and evaluation of those symptoms as illness; or symptom reporting – women may be more likely to recall and report symptoms (Verbrugge, 1985; Ahmed et al., 2009).

2.3. Maternity status

Pregnancy has an impact on drug treatment. Not only are women affected by the drug, but the fetus will also be exposed to ADRs of the drug. There are certain physiologic changes that occur during pregnancy which might affect drug pharmacokinetics and pharmacodynamics, these changes are; total blood

volume increases by 30–40% (1500–1800 ml), extravascular volume increase during the 2nd and 3rd trimester which leads to decreased plasma concentration of iron and some drugs, renal function improves with a renal plasma flow increment of 30% and GFR increases 50%, serum protein 1–1.5 lower; thus renally excreted drugs would have an increased rate of excretion, cardiovascular changes are noted by an increase in cardiac output of about 32% due to an increased heart rate (10–15 bpm) and increased stroke volume, blood pressure is relatively constant. Motility, acidity and tone of GIT are decreased during pregnancy and this might interfere with drug absorption or excretion and finally drug metabolism may be affected at certain stages of pregnancy (Duncombe et al., 2008). Drugs during pregnancy might affect either the mother or the embryo or both. The impact of drugs on fetal organogenesis is crucial because it might lead to teratogenicity and Dysmorphogenesis (Pack et al., 2009). Many drugs for example, antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers pose a risk to the health and normal development of a fetus (Alomar and Strauch, 2010).

2.4. Fetal development

The fetus, which is exposed to any drugs circulating in maternal blood, is very sensitive to drug effects because it is small, has few plasma proteins that can bind drug molecules and has a weak capacity for metabolizing and excreting drugs. Once drug molecules reach the fetus, they may cause teratogenicity (anatomic malformations) or other ADRs (Brundage, 2002). Gestational age is subdivided into three trimesters; first, second and third trimester. The effect of drugs on each trimester is different depending on the degree of fetal development. Drug teratogenicity is most likely to occur when drugs are taken during the first trimester of pregnancy, when fetal organs are formed (Holmes et al., 2001). For drugs taken during the second and third trimesters, ADRs are usually manifested in the neonate (birth to 1 month) or infant (1 month to 1 year) as growth retardation, respiratory problems, infection, or bleeding. Overall, effects are determined mainly by the type and amount of drugs, the duration of exposure, and the level of fetal growth and development when exposed to the drugs. Both therapeutic and nontherapeutic drugs may affect the fetus (Meloni et al., 2009).

2.5. Creatinine clearance category

Creatinine clearance reflects the function of the kidneys which are responsible for the excretion of many drugs. Any change in the renal profile might increase drug toxicity or decrease therapeutic effect. Kidney disease affects drug clearance and metabolism. Venitz (2000) concluded that chronic renal failure affects both renally excreted drugs and also drugs metabolized by the liver through the effect of uremia caused by renal failure. This in turn may affect the disposition of a highly metabolized drug by changes in plasma protein binding and hepatic metabolism. Sun et al. (2006) stated that alterations of drug transporters, as well as metabolic enzymes, in patients with renal failure can be responsible for reduced drug clearance. This reduced metabolic enzyme activity can affect the clearance of the drug (Naud et al., 2008). The effect of renal diseases on non renal drug excretion leads to any disease accompanied with renal insufficiency being affected by this insufficiency and increases the possibility of the appearance of ADRs in that patient.

2.6. Allergy

Drug independent cross-reactive antigens can induce sensitizations, which can manifest as a drug allergy. The existence of such cross-reactivity is supported by medical literature (Chung et al., 2008). After primary sensitization to a causative drug, a second exposure causes affected T cells and antibodies to enter the elicitation phase, corresponding to the type I to IV immune reactions (Gell and Coombs Classification). Most of the drug allergies observed are type I or IV reactions; type II and III reactions are only encountered infrequently (Harboe et al., 2007). The formation of immune complexes, a common event in a normal immune response, usually occurs without symptoms. Rarely, immune complexes bind to endothelial cells and lead to immune complex deposition with complement activation in small blood vessels (Schmid et al., 2006). The clinical symptoms of a type III reaction include serum sickness (e.g., β-lactams), mediation-induced lupus erythematosus (e.g., quinidine), and vasculitis (e.g., minocycline) (Benseler et al., 2007). T-cell-mediated drug hypersensitivity may have a variety of clinical manifestations, ranging from involvement of the skin alone to fulminant systemic diseases. Frequently, the drugs involved are sulfa antibiotics and β-lactams (Ebert et al., 2005).

2.7. Body weight and fat distribution

In the body, drugs are distributed to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue). After a drug is absorbed into the bloodstream, it rapidly circulates through the body. As the blood recirculates, the drug moves from the bloodstream into the body's tissues. Once absorbed, most drugs do not spread evenly throughout the body. Some drugs dissolve in water (water-soluble drugs), such as the antihypertensive drug atenolol. Some drugs tend to stay within the blood and the fluid that surrounds cells (interstitial space). Drugs that dissolve in fat (fat-soluble drugs), such as the anesthetic drug halothane, tend to concentrate in fatty tissues. Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland), because tissues have a special attraction for (affinity) and ability to retain the drug. Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. For example, the anesthetic thiopental, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a water-soluble drug, does not. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs. For some drugs, transport mechanisms aid movement into or out of the tissues (Anderson and Holford, 2008). Some drugs leave the bloodstream very slowly, because they bind tightly to proteins circulating in the blood. Others quickly leave the bloodstream and enter other tissues, because they are less tightly bound to blood proteins. Some or virtually all molecules of a drug in the blood may be bound to blood proteins. The protein-bound part is generally inactive. As the unbound drug is distributed to tissues and its level in the bloodstream decreases, blood proteins gradually release the drug bound to them. Thus, the bound

drug in the bloodstream may act as a reservoir for the drug (Standing et al., 2010). Some drugs accumulate in certain tissues, which can also act as reservoirs of the extra drug. These tissues slowly release the drug into the bloodstream, keeping blood levels of the drug from decreasing rapidly and thereby prolonging the effect of the drug. Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug (Zhao et al., 2009). Distribution of a given drug may also vary from person to person. For instance, obese people may store large amounts of fat-soluble drug, whereas very thin people may store relatively little. Older people, even when thin, may store large amounts of fat-soluble drugs because the proportion of body fat increases with aging (Rhodin et al., 2009).

3. Social factors

3.1. Alcohol drinking

Alcohol affects the metabolism of many drugs and it facilitates the development of ADRs. Alcohol drug interaction refers to the possibility that alcohol may change the intensity of the development of ADRs making it more toxic or harmful to the patient either in a pharmacokinetic or pharmacodynamic manner (Bruce et al., 2008). Taking alcohol with certain drugs can cause many ADRs like nausea, vomiting, headaches, drowsiness, fainting, loss of coordination, hypotension and many other ADRs (Krupski et al., 2009). Internal bleeding may occur due to severe ulceration if alcohol is taken with NSAIDs by a patient having peptic ulcer or ex-peptic ulcer or gastritis (Kim et al., 2009). Chronic alcohol consumption activates enzymes which transform some drugs into toxic chemicals that can damage the liver and other body organs. Alcohol can also magnify the inhibitory effects of sedatives and narcotics at their site of action in the brain. Alcohol might affect the functionality of the liver causing liver cirrhosis and liver hepatitis which in turn affect the ability of this organ to metabolize drugs especially drugs metabolized by the liver and drugs which have first pass metabolism. E.g. the toxicity of beta blockers increases with liver problems (Reuben, 2006). This will lead to drug interactions, because of that physicians and pharmacists must warn patients about the health hazards that might be caused by alcohol drug interaction (Brown et al., 2007). Alcohol drug interaction may be more harmful when elderly patients mix them together, as age and alcohol lead to many health problems (Pringle et al., 2005).

3.2. Race and ethnicity factors

Evidences suggest that ethnicity exerts a substantial influence on drug response and action. Drug action varies greatly between individuals. Ethnic background is controlled by genetic factors, which makes the inter-individual differences due to polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and receptors (Sexton et al., 2000). Recent development suggests that ADRs may be avoided by individualizing the therapeutic plan according to genetics (Meigs et al., 2008). David et al., 2001) suggested genetics play a crucial part in the willingness of some patients to develop ADR for a specific drug over others. A study on epidemiological risk factors for hypersensitivity reactions to abacavir found the Caucasian race as a risk factor for ADRs (Lyssenko et al., 2008). In a recent cohort study Morimoto et al. (2004) evaluated risk factors for ADRs associated with angiotensin-converting enzyme (ACE) inhibitors involving 2225 people of whom 19% had to discontinue therapy due to ADRs, African Americans were found to be more susceptible to developing ACE-related angioedema than other ethnic groups. Ethnicity is an important demographic variable contributing to interindividual variability in medication metabolism and response. Some studies are discussing the issue that genetic factors can determine individual susceptibility to both dose-dependent and dose-independent ADRs. Determinants of susceptibility include kinetic factors, such as gene polymorphisms in cytochrome P450 enzymes, and dynamic factors, such as polymorphisms in drug targets (Cornelis et al., 2009). The relative importance of these factors will depend on the nature of the ADRs; however, it is likely that more than one gene will be involved in most instances (Pirmohamed and Park, 2001). Different ethnic groups have different risks for important ADRs to cardiovascular drugs. Ethnic groups may therefore be one determinant of harm of a given treatment in the individual patient, either because it acts as a surrogate measure of genetic makeup or because cultural factors alter the risk. Black patients had a relative risk of angioedema of 3.0 compared with non-black patients, and the risk of intracranial hemorrhage was higher in black patients than non-black patients (McDowell et al., 2006). These findings may help healthcare providers present more accurate and relevant data to their patients when prescribing cardiovascular therapy. The problem with trials is that the groups of people in trials are not necessary representatives of the general population and if they are, their background might not be specified. It is also documented that the risk of angioedema with blood pressure lowering drugs was three times greater in black patients than non-black patients (Grouzmann et al., 2009). The risk of cough was also nearly three times higher in East Asian patients compared with white patients (Hoffmann and Bier, 2007). For thrombolytic therapy, the risk of bleeding increased 1.5-fold in black patients compared with non-black patients (Mahoney and Devaiah, 2008). Another study shows that 17% of black patients vs. 11% of non-black patients experienced moderate to severe bleeding following thrombolytic therapy; these data come from the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (Coleman et al., 2006). The same study concluded that there was significantly more depression from hydrochlorothiazide (HCTZ) for black patients compared with white patients. Non-whites (namely, black, hispanic, or other) had a higher risk of hospital admission from bleeding after oral anticoagulation for deep vein thrombosis (Kracoff, 2005). Of 58 patients treated with ibutilide fumarate injection for the recent onset of atrial fibrillation or atrial flutter, 3 of 20 (15%) black patients, compared with 1 of 38 (2.63%) white patients, developed Torsade de Pointes after treatment (Regitz-Zagrosek, 2006). Human leukocyte Antigen (HLA) genotype is an essential predictor of the susceptibility of drug-induced liver toxicity. HLA genotype is not the main cause of liver toxicity, there are other genotypes like SLCO1B1 which lead to simvastatin myotoxicity (Daly, 2012). Ten percent of the patients who take Carbamazepine suffer from cutaneous adverse reactions. These ADRs have been attributed to the human leukocyte antigen (HLA)

genotype. In a recent study, it has been determined that carrying HLA-B 1502 in Asians was associated with a pooled odds ratio (OR) of 113.4 for Carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis (Marson et al., 2012). Another recent study showed that patients with ADRs had a higher frequency of CYP1A2 low activity allele combinations (8/12; 67%) and lower CYP1A2-mRNA levels than patients without ADRs (6/22; 27%, $P = 0.019$) (Ferrari, 2012). In Parkinson's disease patients with UDP-glucuronosyltransferase 1A9 genotypes are prone to ADRs and to catechol-*O*-methyltransferase inhibitors (Ferrari, 2012).

3.3. Smoking

Smoking is one of the risk factors of many diseases like peptic ulcer, cancer and cardiovascular diseases (Woo et al., 2009). It also affects the metabolic process by affecting liver enzymes acting as a potent inducer of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1 (Tomlinson et al., 2005). Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacologic effects (Faber and Fuhr, 2005). These drug interactions are not caused by nicotine, the cause is tobacco. Because it stimulates the sympathetic nervous system, nicotine can counter the pharmacologic actions of some drugs (Hukkanen et al., 2005). More research findings worldwide revealed the smoking-drug interaction, and theophylline, flecainide, insulin, oral contraceptives, beta-blockers, thiothixene and H2 blockers are medicines whose therapeutic responses can be affected by smoking (Himmelmann et al., 2003). One clinical study showed that on average insulin-dependent diabetic smokers needed 15–20% more insulin than non-smokers, and up to 30% more if they smoked heavily (Kroon, 2007). Cigarette smoking increases the rate of heparin clearance, possibly because of the smoking-related activation of thrombosis with increases of heparin binding to antithrombin III (Faber and Fuhr, 2005). Cutaneous vasoconstriction by nicotine may decrease the rate of insulin absorption after subcutaneous administration (Schwing et al., 1999). Cigarette smoking also reduces the effect of beta blockers on blood pressure and heart rate (Zevin and Benowitz, 1999).

4. Drug related factors

4.1. Polypharmacy

Taking several drugs, whether prescription or over-the-counter, contributes to the risk of having an ADR. The number and severity of ADRs increases disproportionately as the number of drugs taken increases. Many definitions are applied for polypharmacy. It is different from scholar to scholar but the basic concept of taking more medications at the same time than are clinically appropriate remains constant (Bushardt et al., 2008). It implies to the prescription of too many medications for a particular patient, with a possibility of increased risk of ADRs. The more the medications that are prescribed the more the possibility of polypharmacy, this does not necessarily mean however that patients should not take many medications (Rambhade et al., 2012).

Polypharmacy is a result of many conditions; patients might suffer from more than one disease especially among the elderly. Patients might seek more than one prescriber at the same time for different diseases or acute or chronic conditions. ADRs may occur due to drug interaction, synergism, duplication, additive effect, discontinuation of therapy, changing the dose to save money, skipping some medications and physiological antagonism. One important reason for the development of ADRs from polypharmacy is the inability of some patients especially the elderly to keep track of using their medications regardless of how well the medications may work if given alone. If the patients are not strict enough to take the medications as prescribed, then they will separate from treatment and not take the medication properly. Economic value of the medications may lead to skipping some of them which in turn causes shortage of treatment and the development of adverse events. Prescribing cascade is also a result of polypharmacy in which certain drugs are used to treat the adverse effect of other drugs. This will potentially lead to an endless line of medications used by the patient. It is possible that symptoms and signs of polypharmacy could be overlooked by confusing them with symptoms of aging or the disease itself. This in turn will result in more medications being taken by the patients. Constipation, diarrhea, tiredness, weakness, skin rashes, falls, anxiety and many other symptoms could be caused by both diseases and polypharmacy. A study among 65 year old patients and older in the United States of America found that in more than 40% of the patients involved in the study there was evidence of incorrect medication use, overuse and underuse for those treated by more than five medications (Steinman et al., 2006). The risk of dementia increases steadily with the number of medications used and age in older people as described in a study in Taiwan (Lai et al., 2012). 'In another study of the frequency of polypharmacy with three or more medications at hospital discharge for bipolar disorders or unipolar depression, polypharmacy increased from 3.3% of patients (1974–1979), to 9.3% (1980–1984), to 34% (1985–1989), and to 43.8% (1990–1995)' (Hoffman et al., 2011). Another study regarding the development of Acute Renal Failure (ARF) as a result of polypharmacy indicated that 'relative to patients who received polypharmacy for less than 30 days, those who received polypharmacy for 31–90, 91–180 and over 181 days had odds ratios of developing ARF of 1.33 ($p < 0.001$), 1.65 ($p < 0.001$) and 1.74 ($p < 0.001$), respectively (Chang et al., 2012)'.

Drug interactions play a very important role in the development of polypharmacy and can be defined as the modulation of the pharmacologic activity of one drug by the prior or concomitant administration of another drug. It is also defined as an interaction which occurs when the effects of one drug are changed by the presence of another drug (Kaufman et al., 2002). The causes and significance of drug interactions are multifaceted and include drug dose, serum drug level, route of administration, drug metabolism, duration of therapy, and patient factors, such as age, gender, weight and genetic predisposition (Heuberger, 2012). Drug interactions are often classified as either pharmacodynamic or pharmacokinetic interactions. Pharmacodynamic interactions include those that result in additive or antagonistic pharmacological effects (Wildinson et al., 2010). Pharmacokinetic interactions involve induction or inhibition of metabolizing enzymes in the liver or elsewhere, displacement of drug from plasma protein binding sites, alterations in gastrointestinal absorption, or competition for active renal secretion. The frequency and prevalence of

interactions is dependent upon the number of concomitant drugs and the complexity of the regimens (Wildinson et al., 2010). The prevalence is also dependent upon other variables, such as patient adherence, hydration and nutritional status, degree of renal or hepatic impairment, smoking and alcohol use, genetics and drug dosing. Additionally, some patients may exhibit evidence of a particular drug interaction, while others with the same drug combination do not (Obreli-Neto et al., 2012). The addition of nonprescription medications plays a very important role in causing ADRs. Some studies indicate that patients aged >65 years use on average 2–6 prescribed medications, and 1–3.4 nonprescribed medications (Routledge et al., 2003). It is a well established fact that non prescription medications are most commonly used among the geriatric population (Prybys et al., 2002). A drug combination may sometimes cause synergistic toxicity, which is greater than the sum of the risks of toxicity of either agent used alone (Harugeri et al., 2011). Patients concurrently receiving corticosteroids and NSAIDs had a risk of peptic ulcer disease that was 15 times greater than that of nonusers of either drug (Routledge et al., 2003). The concurrent use of antidepressants, hypnotics, antiepileptics and antihistamines may lead to more drowsiness (Nidhi, 2012). Both vancomycin and narcotics induce dose-dependent skin reactions and synergize to cause adverse reactions (Yeon et al., 2011). Prescribing cascade occurs when patients take a medication and suffer from some adverse drug reactions that are misdiagnosed by the physicians as symptoms of a disease, requiring more medication. This condition may lead to either worsening of the ADR or putting patients at risk of new ADRs. Antihypertensives, Sedatives, Opioids, NSAIDs, Antiepileptics, Antibiotics and herbal medications are some of the most frequently prescribed drugs. The cascades include the use of prochlorperazine to prevent drug-induced dizziness, antihypertensives to treat NSAID-induced hypertension and levodopa to manage metoclopramide-induced movement disorder (Kalisch et al., 2011). Prochlorperazine for instance may cause postural hypotension which may exacerbate any hypotensive effect of antihypertensive drugs. This cascade might be the cause of hip fracture following the use of prochlorperazine (Caughey et al., 2010). ACEIs induced cough may be misinterpreted as a chest infection and given antibiotics and cough suppressant. Thiazide diuretics may cause hyperuricemia which leads to prescribing colchicines which in turn may cause diarrhea (Rochon and Gurwitz, 1997). Erythromycin may cause arrhythmia and be misinterpreted as a disease and given antiarrhythmics (Corrao et al., 2005). Antiepileptics may cause a rash which leads to corticosteroid use (Tsiropoulos et al., 2009). Using therapeutic equivalents to treat the same illness is considered one of the causes of ADRs, two analgesics, antihistamine with other sedative drugs or two antihypertensives are some examples of using two medications which exhibit the same action. Lack of coordination between physicians, pharmacists and patients can in turn lead to redundancy, using the same medications under different brand names. This will increase the risk of ADRs. Finally; some studies indicate that polypharmacy might affect the nutritional status of patients which leads to malnutrition (Zdenek et al., 2013) which is more pronounced among the older population. Polypharmacy should be looked at seriously in order to prevent potential ADRs which affect patient health status, compliance and therapeutic outcomes.

4.2. Drug dose and frequency

Drug dosing affects the development of ADRs in many ways; e.g. some drugs need to be given in the morning and others in the evening, some at bedtime. Taking Bisphosphonates at bed time may lead to esophagitis, the antiplatelet effect of aspirin when taking in the evening is more potent that in the morning (Hermida et al., 2005). Dosing needs to be considered as a factor which might have some effect on the development of ADRs.

5. Disease related factors (accompanied diseases)

Concomitant patient's disease may also influence susceptibility to ADRs. For example; increases of the frequency of idiosyncratic toxicity with anti-infective drugs such as trimethoprim-sulphamethoxazole (Hanses et al., 2009). Multiple diseases make patients more vulnerable to ADRs due to the presence of many diseases and the use of many drugs. If hypertension is accompanied with other diseases, these diseases might have an impact on the response of the body to antihypertensive drugs since the metabolic processes of the body will be affected negatively. 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. The same issue occurs in patients with peptic ulcer disease, many drugs including NSAIDS when prescribed, may lead to serious medical problems (Daneshtalab et al., 2004). Multiple diseases are a very important factor which causes drug-disease interactions and ADRs. Drugs that are helpful in one disease are harmful in another. For example, some beta-blockers taken for heart disease or high blood pressure can worsen asthma and make it hard for people with diabetes to tell when their blood sugar is too low. Some drugs taken to treat a cold may worsen glaucoma. Diabetes, high or low blood pressure, an ulcer, glaucoma, an enlarged prostate, poor bladder control, and insomnia are particularly important, because people with such diseases are more likely to have drug-disease interactions (Kurnik et al., 2004). Certain drugs have the capability to exacerbate acute and/or chronic disorders. These drugs can also blunt the typical signs and symptoms of a hypoglycemic reaction in diabetic patients and alter insulin utilization in the body (Peng et al., 2002). These drugs and calcium channel blockers, particularly verapamil, have negative inotropic and negative chronotropic effects on the heart and can exacerbate diseases such as congestive heart failure (Ariyo et al., 2000). Prednisone can aggravate congestive heart failure and cause fluid retention. Because some of these interactions may have an insidious onset, careful and close medical attention is mandatory (Boer et al., 2003). AIDS for instance worsen ADRs, the incidence of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) has been reported to be higher among those particular patients. A study shows that one of the medications taken among patients who developed TEN AND SJS is trimethoprim/sulfamethoxazole (Mittman et al., 2012). According to a recent study of a multivariate logistic regression indicated that a T CD4+ count of <200 cells/mm^3 increased the risk of hepatotoxicity by a factor of 1.233 ($p < 0.001$) and that coinfection with hepatitis B or C virus increased this risk by a factor of 18.187 ($p = 0.029$) (Lima and Melo, 2012).

6. Conclusion

Different factors affect the development of ADRs in different degrees, some of these factors have a direct effect on ADRs, others are insidious. Serious attention to these factors will result in preventing or reducing the occurrence of unwanted drug actions which could have been avoided if health care providers spent enough time to pinpoint these problems. Health education, counseling and reconciliation are tools that must be utilized by pharmacists. Information technology should also be part of the medication decision making process which provides health professionals with up to date knowledge of drug-dosing, interaction, ADRs and other important information needed to use medication in the optimum manner. The elderly should also be the focus of the pharmacist, because they form the majority of those who uses polypharmacy. Finally; for each benefit to come out of a medication there is always a possibility for some risks; benefits should always outweight risks for the purpose of providing the best treatment with the least number of medications at the most economic price.

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