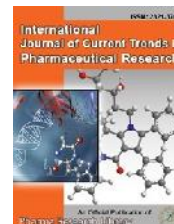




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Review Article

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A Review on Study of Adverse Drug Reactions in Hospitalized Patients

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ABSTRACT

ADRs are one of the leading causes of morbidity and mortality in healthcare. 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. 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, for each benefit to come out of a medication there is always a possibility for some risks; benefits should always outweigh risks for the purpose of providing the best treatment with the least number of medications at the most economic price.

Keywords: ADR, polypharmacy, symptoms of disease, risks and antihypertensives

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1. Introduction

ADRs are one of the leading causes of morbidity and mortality in healthcare. According to the latest survey by Institute of Medicine, they reported that between 44,000 and 98,000 deaths occur annually from medical errors. Of International Journal of Current Trends in Pharmaceutical Research

this total, an estimated 7000 deaths occur due to ADRs. Analyzing 39 studies of the American pharmaceutical system over four decades found that, 13,06,000 people died as a result of ADRs. More than 2 million suffered serious

side effects. 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. In another survey conducted by the American Society of Health-System Pharmacists, 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 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.

Pharmacovigilance involves the study of drug-related injuries, making warning or withdrawal recommendations for pharmaceutical agents; it encompasses the detection, assessment, understanding, and prevention of ADRs. Pharmacists play a vital role in every step of the pharmacovigilance process, which can prevent patients from undergoing unnecessary procedures or taking unwarranted drugs. In addition to preserving the safety and quality of life for the patient, pharmacovigilance can represent a cost savings to the patient and the health care institution. By reporting known or suspected ADRs, pharmacists, other health care practitioners, and patients can assist in identifying patterns and trends, which may lead to increased regulatory scrutiny or even the withdrawal of drugs that do not have a favorable risk-benefit ratio.

2. 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. 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 patient should not take many medications. 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.

The risk of dementia increases steadily with the number of medications used and age in older people as described in a study in Taiwan. '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 (2003–2013), to 12.3% (1992–2002), to 34%. 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.

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. 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. Drug interactions are often classified as either pharmacodynamic or pharmacokinetic interactions. Pharmacodynamic interactions include those that result in additive or antagonistic pharmacological effects. 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. 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. 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 non prescribed medications. It is a well established fact that non prescription medications are most commonly used among the geriatric population. A drug combination may sometimes cause synergistic toxicity, which is greater than the sum of the risks of toxicity of either agent used alone. 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. The concurrent use of antidepressants, hypnotics, antiepileptics and antihistamines may lead to more drowsiness. Both vancomycin and narcotics induce dose-dependent skin reactions and synergize to cause adverse reactions. 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.

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. 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. Erythromycin may cause arrhythmia and be misinterpreted as a disease and given antiarrhythmics. Antiepileptics may cause a rash which leads to corticosteroid use. 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 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.

3. 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 than in the morning. Dosing needs to be considered as a factor which might have some effect on the development of ADRs.

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. 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. 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. 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. 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. 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.

4. Conclusion

Different factors affect the development of ADRs in Hospitalized patients, 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 outweigh risks for the purpose of providing the best treatment with the least number of medications at the most economic price.

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