

**FROM EVOLUTION TO PREVENTION OF ADVERSE DRUG REACTION**

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***Corresponding author e-mail:** angeline_3012@yahoo.com**ABSTRACT**

It is an overview of adverse drug reaction where its evolution and various classes of adverse drug reaction are being explained. Also, how patient and drugs can be factors contributing to the occurrence of adverse drug reaction are discussed here. Not only that, there are also different pathways in which adverse drug reaction can be monitored and reported to improve pharmaceutical care. The role of healthcare professionals, physicians, pharmacists and patient in averting adverse drug reaction is also being described in brief.

Keywords: Adverse drug reaction, Evolution, Types, Factors, Monitoring, Prevention**INTRODUCTION**

Adverse drug reaction (ADR) is one of the most common health issues arising from the medication use whether it is appropriate or inappropriate one.^[1] Adverse drug reaction has imposed serious health complication that may or may not be fatal to the medication users. ADR was first discovered, reported and documented in the year 1960, when Thalidomide was withdrawn from the US market due to its serious birth defects. Childbearing women consuming Thalidomide for the purpose of reducing or preventing morning sickness unfortunately give birth to incomplete formed fetus, a condition known as phocomelia.^[2] Refer to Figure 1. This tragedy leads to the stronger drug regulation of Food and Drug Act in 1962. Since then, every drug before being marketed has to be approved by the Food and Drug Administration (FDA) to ensure its safety and effectiveness. Findings have shown various factors like patient related and drug related that led to the adverse drug reactions. ADR can be classified into few classes and it is very important that these events to be reported monitored and prevented to avoid condition that may harm the medication users.

Definition of ADR

According to the World Health Organization, in 1975, ADR has been defined as a response that is

noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological functions.^[3] ADR can also be simply described as any unwanted effect resulting from a drug's use in treatment. FDA also termed adverse drug reaction or serious drug event as an event relating to drugs or devices, as one in which the patient outcome is death, life-threatening, hospitalization, disability, birth defects (congenital abnormalities), or required intervention to prevent permanent impairment or damage.^[4]

Evolution of ADR

The first incidence (even before Thalidomide disaster) related to ADR was on 29 January 1848, where a girl named Hannah Greener died after being given an anesthetic, Chloroform (introduced in the year 1847) before a surgery for the treatment of an in-growing toe nail. Her death was found to be due to the episodes of ventricular fibrillation caused by Chloroform. Although that incidence was reported by *The Lancet* journal, however there wasn't a proper system to retain the adverse drug reaction, till the Thalidomide disaster.^[5]

In the 20th century many potent drugs were introduced with an increase in the frequency and severity of the adverse drug reaction. The next famous incident that took place before Thalidomide

disaster was the Sulfanilamide disaster that killed more than 100 people.^[6] This incident that occurred in the year 1937 was later found out to be due to the inclusion of a lethal solvent known as diethyl glycol (DEG).^[7] DEG is a clear, colorless, practically odorless, viscous, hygroscopic liquid with a sweetish taste that is used in wide range of industrial products. Following ingestion, DEG is converted to its active metabolite 2-hydroxyethoxyacetic acid (HEAA) that is a major contributor to renal and neurological toxicities.^[8]

Almost 1000 drug products were marketed in between 1952 and 1960. The Thalidomide disaster in 1960 drew worldwide attention and it prompted the UK Government to set up an advisory committee in 1962 to ensure the safe and effective use of drug. The establishment of Committee on Safety of Drugs (CSD) led to the very famous scheme that is used till now in ADR reporting known as Yellow Card Scheme (will be discussed later). This scheme was earlier set up by its highly-regarded first chairman Sir Derrick Dunlop in 1964.^[5]

Since then, quite number of drug product has been withdrawn from the market due to various reasons. For example, the appetite suppressant, Meridia[®] (Sibutramine) is withdrawn from the US market due to increase in cardiovascular and stroke risk in patient.^{[9][10]} Besides this, there are many drugs that were recalled due to various adverse drug reactions as listed in the FDA website. Recently, in 2011, the drug Xigris[®] (Drotrecogin alfa (activated)) was withdrawn since there is no survival benefit proven.^[11]

Causes of ADR

The occurrence of ADR may be due to four factors which include patient related factors, drug related factors, social factors and disease related factors. However, this article focuses mainly on the first two vital factors.^[12]

Patient related factors

Age: ADR occur in different age group of people. A study shows that ADR is common in elderly patient and it is preventable in ambulatory clinical setting.^[13] Elderly people and very young patient aged one to four years old are susceptible to the ADR because clinical trials do not focus on them. Also, due to the poorly developed physiology in infants, thus their capability to metabolize the drug less. On the other hand, as the age goes up, liver loses its ability to metabolize the drug, and kidney is less able to excrete the drug, thus leading to ADR.^{[14][15]}

Gender: ADR frequently occur in women when compared to men. Studies has proven the reason

behind this that is the hepatic microsomal enzyme CYP 450 particularly the CYP 3A4 is more active in women than in men. This leads to differences in the drug metabolism process.^[16] The anatomical and physiological differences such as body weight, body composition, liver and renal function between women and men affect the pharmacodynamic as well as pharmacokinetics aspects of the drug. This may lead the occurrence of ADR.

Pregnancy: During pregnancy, certain physiological changes may occur in the women's body that may alter the pharmacodynamics and pharmacokinetics profile of the drug thus affecting the fetus inside the womb. For an instance, the motility, acidity and the gastrointestinal tone may be decreased during pregnancy and this may interfere with the ADME (absorption, distribution, metabolism and excretion) of a drug.^[17] Some drugs like angiotensin converting enzyme (ACE) inhibitors, Lithium and Isotretinoin may impose teratogenic effect in developing fetus.^[18]

Renal creatinine clearance level: The major organ responsible for the excretion of drug metabolite is the kidney and this is often measured through the creatinine clearance level. Patient with kidney disease is most likely to experience drug toxicity due to their kidney's inability to excrete the drug metabolite. In addition, the alteration of the drug transporters and metabolic enzymes take place in patient with renal failure causing a decrease in the creatinine clearance.^[19]

Distribution of fats: Prior to the administration of drugs, they are distributed to all parts of the body through bloodstream. Before distribution, these drugs have to be absorbed. Water-soluble drugs may readily dissolve in the body fluid while fat-soluble drugs may take time to dissolve as they tend to concentrate more on the fatty tissues to be absorbed.^[20] For fat-soluble drugs, plasma protein-binding plays a crucial role. Highly plasma protein-bound drug leave the bloodstream and enters the bloodstream more slowly compared to lowly bound ones. Accumulation of the drugs in certain tissues acts as drug reservoir, releasing the drug slowly into the bloodstream, maintaining the plasma drug concentration and thereby extending the effect of the drug. However, this sometime can be fatal when the drugs keep circulating in the body even after the drug is discontinued.^[21]

Drug-related factor

Polypharmacy: Many scholars define polypharmacy in different context. It can be considered as when a patient takes more than five medications. Duplication

of medication is also termed as polypharmacy. Frequently, polypharmacy is defined as medication taken that does not match the diagnosis.^[22] Various factors actually contributes to the occurrence of polypharmacy, one of which include when patient seek more than one prescriber at the same time for different disease (easy access to health care). Failure of the patient, especially the elder ones, to keep track of the medications regardless of how well the medication may work if given alone, is one of the contributors for the development of ADR from polypharmacy.

Drug interaction that arises from polypharmacy may also add to the occurrence of ADR. The frequency and prevalence of drug interaction relies on the number of concomitant drugs as well as the complexity of the drug regimen.^[23] The usage of non-prescription medication is very common among geriatric patients that bring about an increase in ADR when compared young patients.^[24] When two drugs are administered together, it may sometimes cause synergistic toxicity which is greater than the sum of the risks of toxicity of either agent used alone. For example, the concomitant use of antidepressants, antiepileptics, antihistamines and hypnotics may cause severe drowsiness.^[25]

Classification of ADR

ADR can be broadly categorized based on Rawlins and Thompson classification, Wills and Brown classification, and its severity.

Rawlins and Thompson classification^[26]

Here, ADR can be divided into two main headings which are Type A and Type B. Type A reactions are commonly occurring, predictable, reactions related to the pharmacological action of the drug. They are usually dose dependent. Examples of Type A reaction include the following:^[27]

- 1) *Drug overdose* – overdose of Paracetamol may lead to hepatotoxicity and occurrence of hypoglycemia with Sulfonylurea
- 2) *Side effects* – nearly unavoidable reactions produced by the normal therapeutic dose such as sedative effect caused by antihistamines.
- 3) *Secondary effects* – they are secondary pharmacological effect like development of diarrhea with antibiotics therapy due to altered gastrointestinal bacterial flora.
- 4) *Drug interaction* – reaction produce when two drugs are concomitantly administered where they affect each other's response either pharmacologically or kinetically.

On the other hand, Type B reactions are those unpredictable ones and they are dose independent.

They occur less commonly and mostly are unrelated to known pharmacological action of the drug. Examples of Type B reaction include the following:^[28]

- 1) *Drug intolerance* – lower threshold to normal pharmacological action of a drug such as tinnitus that occur at single average dose of aspirin.
- 2) *Drug allergy/ hypersensitivity reaction* – refers to immune mediated response (eg: anaphylaxis) to a drug agent (Penicillin) in sensitized patient.
- 3) *Pseudoallergic reaction* – a reaction with same clinical manifestations as an allergic reactions like direct mast cell activation and degranulation by drugs (opiates and vancomycin).
- 4) *Idiosyncratic reactions* – an uncommon and abnormal response to drug usually due to genetic abnormality that affect the drug metabolism and receptor sensitivity.

However, there were few limitation associated with Rawlins and Thompson classification of ADR. First, some of the ADRs do not fit in either category and hence, it is difficult to determine whether the reaction falls under Type A or Type B. Secondly, when a reaction is not classified as Type A, then it is automatically considered as Type B reaction, leading to highly heterogenous group little in common.^[29]

Wills and Brown classification^[30]

To overcome the limitation, Wills and Brown introduced a new classification of ADR, in which ADR are classified into nine different types. They are as follow:

- 1) Type A (Augmented)

The reactions are relatively common and can be predicted. They are dose dependent and the condition can be improved if the drug is withdrawn. Eg: bradycardia associated with β -blockers.

- 2) Type B (Bugs)

Similar to Type A in which they are predictable and the reaction improves when the agent is discontinued. Type B reaction involves the interaction with the microorganisms. Eg: oral thrush cause by broad spectrum antibiotics.

- 3) Type C (Chemical)

They are not pharmacologically predictable, but may be seen based on the knowledge of physicochemical characteristics of the drug. Type C reactions are irritant reaction that is related to drug concentration. Eg: contact dermatitis.

- 4) Type D (Delivery)

Type D reactions are independent of the chemical as well as pharmacological properties of the drug. Instead, they occur due to method of administration

or nature of the drug formulation. Eg: infection at the site of injection.

5) Type E (Exit)

The reactions are pharmacologically predictable and begin only when the drug is withdrawn or the dose is reduced. The condition of the patient improves when the drug therapy is reintroduced. Eg: withdrawal seizure when anticonvulsants like Phenytoin is withdrawn.

6) Type F (Familial)

They only occur in genetically predisposed patient. Eg: hemolytic anemia with primaquin in G6PD deficient individuals.

7) Type G (Genotoxicity)

Irreversible genetic damage is caused by this Type G adverse reaction. Eg: teratogenic agent like Thalidomide causes genetic damage to the developing fetus.

8) Type H (hypersensitivity)

They are also known as drug allergy and is often immune mediated response. Hypersensitivity reaction can be further classified into few types as in Table 1.

9) Type U (Unclassified)

This includes those reactions in which the mechanism is unclear. Eg: taste disturbances associated with Simvastatin.

Classification of ADR based on its severity^[31]

The severity of ADR can be categorized into 4 which are mild, moderate, severe and lethal. *Mild* adverse reactions are those in which no antidote or treatment is required and also hospitalization is not required. For instance, constipation caused by opioids. On the other hand, the *moderate* adverse reaction requires treatment where doses may be modified, but there is no necessity for the therapy to be discontinued. Also, hospitalization may be prolonged for the patient with moderate adverse reaction. Venous thrombosis caused by hormonal contraceptive falls under this category. Moving on to *severe* adverse drug reaction, they are potentially life threatening. It is recommended to discontinue the drug therapy and special treatment is required. For example, angioedema caused by ACE inhibitors like Enalapril. Lastly is the *lethal* adverse drug reaction that may bring about death either directly or indirectly. This includes hemorrhage due to anticoagulants and liver failure associated with overdose of Paracetamol.

Monitoring and Reporting of ADR

The occurrence of ADR has brought about many impacts on a countries development (Pharmacoeconomics), society as well as quality of life. The rate of morbidity and mortality keeps increasing due to ADR, especially in a poorly developed country and countries in transition. This is

due to lack of information available on ADR, lack of legislation and proper drug regulation which includes ADR reporting. Consequently, irrational drug use by healthcare professionals and patient takes place.

Before every product come into the market, it has to undergo some clinical trials to ensure its safety and effectiveness to be used in human being. However, the effect of the drug studied during the four phases of clinical trial does not truly reflect its effectiveness while being used in hospitals after being marketed. Even how well the pre-clinical work in animals and patients are done, yet, certain adverse effects of drugs may only be detected when a large number of populations receive them. So, now appear the crucial role of pharmacovigilance.

In 2002, the World Health Organization (WHO) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. It provides the necessary information to the users to optimize the safe and effective use of any products. Prevention of patient being affected unnecessarily by the negative consequences of pharmacotherapy is the ultimate outcome of pharmacovigilance.^[32]

Every country has its own way of detecting, monitoring and reporting adverse drug reactions. For example, in Malaysia, the National Adverse Drug Reaction Monitoring Centre and the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) is responsible for handling adverse drug reaction cases. In Canada, there is a guideline introduced in monitoring ADR which is Canadian Adverse Drug Reaction Monitoring Program that help the Canadian to report any ADR encountered. There are approximately 10,000 domestic adverse event reports submitted annually. All information on domestic adverse events is maintained in a computerized database.

ADR reporting can also be done through Medicine and Healthcare products Regulatory Agency (MHRA) situated in United Kingdom (UK). A Drug Analysis Prints give a complete listing of all UK spontaneous suspected adverse drug reactions (ADRs) reported through the Yellow Card Scheme to the MHRA and the Government's independent scientific committee on medicines safety, the Commission on Human Medicines (CHM). Yellow card reports are submitted to MHRA via telephone, post or internet. MHRA electronically records and reviews information submitted so that important safety issues can be detected.^[33] Yellow card scheme came into existence after the Thalidomide tragedy in 1964, and was initially restricted to doctors. Over the years the scheme has been expanded to include

pharmacists, nurses, dentists and coroners, and is even starting to be piloted for patients.^[34]

In addition to that reporting of ADR can also be done to the FDA Adverse Event Reporting System (FAERS), a database that contains information regarding adverse drug reactions as well as medication error that was reported to FDA. This helps in support of the FDA's surveillance program for therapeutic goods. The adverse drug reaction reports are circulated to healthcare professionals and public through 'MedWatch' program.^[35] The United States FDA (USFDA) in its official website shows the statistics of ADR reports received and entered into FAERS as of December 31, 2013. Refer to Figure 2 below.

Prevention of ADR

It is the responsibility of every individual including healthcare professionals, physicians, pharmacists as well as patient, to play their role effectively in preventing adverse drug reaction from taking place. This is so to reduce the rate or morbidity that has increased for the past years.

- Nurses being the first person to observe the inpatient have to be alert all the time at their duty. A full drug history of the patient has to be obtained including those of the prescription and non prescription medications and herbal products. It is important to question the patient if they have any allergy, and prior to that the nurse should have enough knowledge to be able to differentiate between side effects and adverse drug reactions. An essential step the nurses should take is that to report to the respective regulatory authority about any adverse drug reaction that has occurred or even if it's a suspicious one. Also, it is advisable for all the healthcare professionals to be actively involved in any ADR monitoring and reporting program.^[29]
- Besides patient care, supplying adequate information on suspected adverse drug reaction is also a moral duty of the physician in minimizing ADRs. If any adverse drug reaction has occurred, physician must be able to decide on the right treatment to be given, especially in emergency cases. Physicians have to ensure they are up-to-date with the current issue relating to ADR occurring worldwide. They also have to keenly participate in ADR reporting program.^[29] It is also recommended for the physicians to prescribe

as few drugs as possible and give clear instructions to avoid ADR.

- Pharmacists also play an important role in averting ADR. They are to exert leadership in the development, maintenance and ongoing evaluation of ADR programs.^[35] Educating the other healthcare professionals and encouraging the compliance with ADR program is one of the responsibility of a pharmacist in minimizing ADR. Pharmacists should be able to analyze the reported ADR and find ways to solve them. To do this, they may communicate with other healthcare professionals as well. The drugs and patient that are at high risk of being involved in ADR are to be identified by the pharmacist, so that preventive measure can be taken to avoid complications. Pharmacists are required to report serious ADR to the FDA and be involved in publication as well as presenting chief ADRs to the community. Dose adjustment may be required for patient with hepatic and renal disease as it may impair the clearance of drugs from the body. Thus, pharmacist must be able to decide and advice the physician on the dosing regimen for the patient.
- Patient can also help in preventing ADR by avoiding polypharmacy. If they have more than one prescriber, then it is a must for them to make sure each one knows what the other is prescribing. Patient are also required to know well the medication they are taking and be cautious with any associated ADR that has been warned by the physician or pharmacist. They are encouraged to participate in ADR reporting program like the MHRA through Yellow Card Scheme.

Conclusion

ADR has been a major problem in the healthcare system since 1848. Therefore it is the responsibility of all healthcare workers to develop strategies to report, monitor and prevent ADR. An effective ADR monitoring program should be establish in all countries to improve patient's quality of life. Ultimately, an ongoing ADR monitoring and reporting program may help to measure the economic impact of ADRs prevented, as manifested through reduced hospitalization, efficient and economical drug use, and minimize organizational liability. A well established ADR monitoring system will benefit the healthcare system if a team of dedicated and expertise people are formed. .

Figure 1: Image related to Thalidomide tragedy

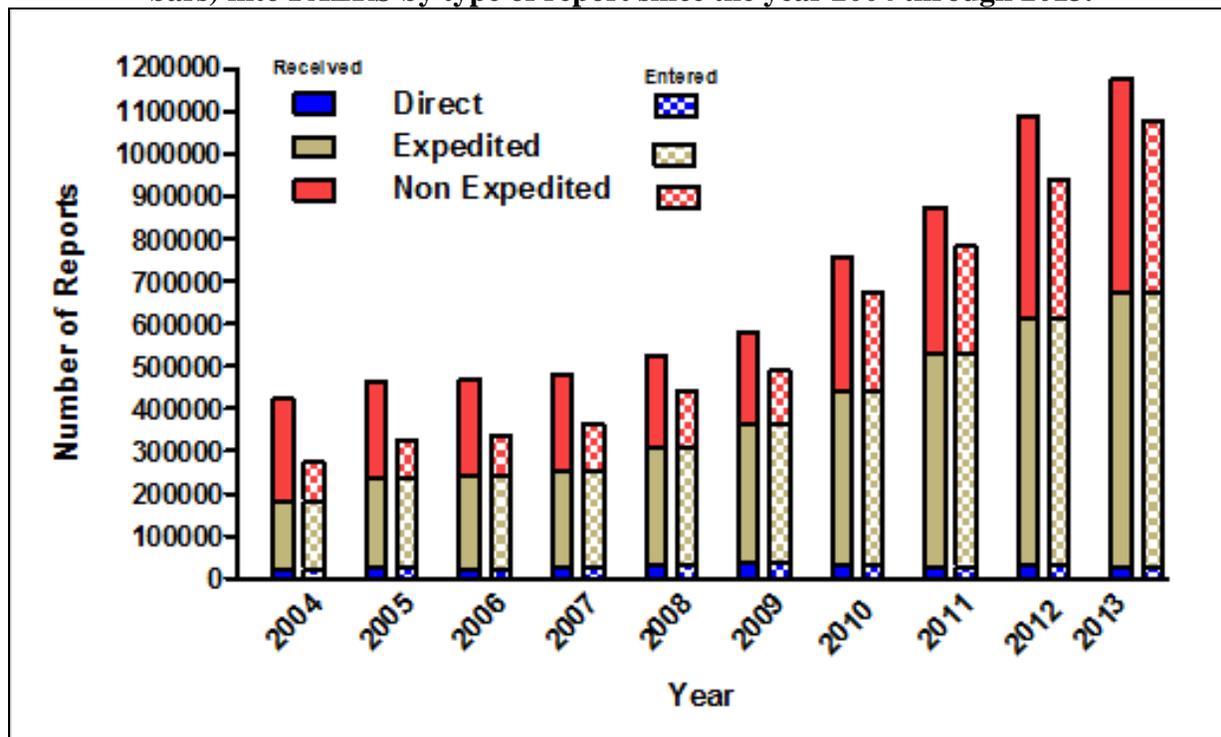


Table 1: Gell and Coombs Classification of Drug Hypersensitivity Reactions

<i>Immune reaction</i>	<i>Mechanism</i>	<i>Clinical manifestations</i>	<i>Timing of reactions</i>
Type I (IgE-mediated)	Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators	Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis	Minutes to hours after drug exposure
Type II (cytotoxic)	Specific IgG or IgM antibodies directed at drug-hapten coated cells	Hemolytic anemia, neutropenia, thrombocytopenia	Variable
Type III (immune complex)	Tissue deposition of drug-antibody complexes with complement activation and inflammation	Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis	1 to 3 weeks after drug exposure
Type IV (delayed, cell-mediated)	MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release	Allergic contact dermatitis, maculopapular drug rash*	2 to 7 days after cutaneous drug exposure

MHC = major histocompatibility complex.
 *—Suspected Type IV reaction, mechanism not fully elucidated.

Figure 2: Illustration of the number of reports received (solid bars) and entered (checked bars) into FAERS by type of report since the year 2004 through 2013.



REFERENCES

1. Marca A. Reidi, Adrian M. Casillas. Adverse Drug Reactions: Types and Treatment Options. American Family Physician, 2003; 68(9).
2. Lary JM, Daniel KL, Erickson JD, Roberts HE, Moore CA. The return of thalidomide: can birth defects be prevented? Drug Saf. PubMed, 1999 September; 21(3): 161-9.
3. Requirements for adverse reaction reporting. Geneva, Switzerland. World Health Organization, 1975.
4. Kessler DA. Introducing MedWatch, using FDA form 3500, a new approach to reporting medication and device adverse effects and product problems. Journal of American Medical Association (JAMA), 1993; 269: 2765-8.
5. The evolution of pharmacy, Theme E, Level 3 Adverse drug reaction reporting. Royal Pharmaceutical Society, 2015.
6. Kevin Outterson, J.D. Regulating Compounding Pharmacies after NECC. The New England Journal of Medicine, 2012 November 22; 367(21).
7. Jerry Avorn, M.D. Two Centuries of Assessing Drug Risks. The New England Journal of Medicine, 2012 July 19; 367(3)
8. Leo J. Schep, Robin J. Slaughter, Wayne A. Temple, and D. Michael G. Beasley. Diethylene glycol poisoning. Journal of Clinical Toxicology, 2009 July; 47(6): 525-535.
9. Andrew Pollack. Abbott Labs Withdraws Meridia, Its Diet Drug, From the Market. The New York Times, Saturday October 9, 2010; B3.
10. W. Philip T. James, M.D., D.Sc, Ian D. Caterson, M.D., Ph.D., Walmir Coutinho, M.D., D.Sc., Nick Finer, M.B., B.S., Luc F. Van Gaal, M.D., Ph.D., Aldo P. Maggioni, M.D., Christian Torp-Pedersen, M.D. Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects. The New England Journal of Medicine, 2010 September 2; 363(10).
11. Xigris (drotrecogin alfa): withdrawal & recall, Australia. Department of Health, Therapeutics Good Administration, 2011 October 26.
12. Muaed Jamal Alomar. Factors affecting the development of adverse drug reactions (Review article). Saudi Pharmaceutical Journal, 2014; 22: 83-94.

13. Debellis, K., Field, T.S., Gurwitz, J.H., Harrold, L.R., Rothschild, J., Seger, A.C. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*, 2003; 289 (9): 1107–1116.
14. Budnitz, D.S., Shehab, N., Kegler, S.R., Richards, C.L. Medication use leading to emergency department visits for adverse drug events in older adults. *Annals of Internal Medicine*, 2007; 147: 755–765.
15. Jimmy, J., Padma, G.M.R. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacological Research*, 2006; 54: 226–233.
16. El-Eraky, H., Thomas, S.H.L. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. *British Journal of Clinical Pharmacology*, 2003; 56: 198–204.
17. Duncombe, D., Wertheim, E.H., Skouteris, H., Paxton, S.J., Kelly, L. How well do women adapt to changes in their body size and shape across the course of pregnancy. *Journal of Health Psychology*, 2008; 13(4): 503–515.
18. Marleen M.H.J. van Gelder, Iris A.L.M. van Rooij, Richard K. Miller, Gerhard A. Zielhuis, Lolkje T.W. de Jong-van den Berg, and Nel Roeleveld. Teratogenic mechanisms of medical drugs. *Human Reproduction Update*, 2010; 16(4): 378–394.
19. Sun, H., Frassetto, L., Benet, L.Z. Effects of renal failure on drug transport and metabolism. *Pharmacology & Therapeutic Journal*, 2006; 109(1–2): 1–11.
20. Nai-Ning Song, Shao-Yu Zhang, Chang-Xiao Liu. Overview of factors affecting oral drug absorption. *Asian Journal of Drug Metabolism and Pharmacokinetics*, 2004; ISSN 1608-2281-0403-00167-10.
21. Zhao, W., Elie, W., Roussey, G., Brochard, K., Niaudet, P., Leroy, V. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. *Clinical Pharmacology & Therapeutics*, 2009; 86(6): 609–618.
22. Bergman-Evans B. Evidence-based guideline. Improving medication management for older adult clients. *Journal of Gerontological Nursing*, 2006; 32: 6–14.
23. Wildinson, G.R., Goodman, Gilman's. *The Pharmacological Basis of Therapeutics*. 12th edition, New York; McGraw-Hill: 2010.
24. Prybys, K.M., Melville, K.A., Hanna, J.R., Gee, P.A. Polypharmacy in the elderly: clinical challenges in emergency practice: part I: overview, etiology, and drug interactions. *Emergency Medicine Reports*, 2002; 23 (11).
25. Nidhi, S., Concept of drug interactions. *International Research Journal of Pharmacy*, 2012; 3(7).
26. Jeffrey K Aronson, Robin E Ferner. Joining the DoTS: new approach to classifying adverse drug reactions. *British Medical Journal*, 2003 November 22; 327: 1222-1225.
27. Marc A. Riedl, M.D., And Adrian M. Casillas, M.D. Adverse Drug Reactions: Types and Treatment Options. *American Family Physician*, 2003 November 1; 68(9).
28. Daniel Vervloet, Stephen Durham. ABC of allergies: Adverse reactions to drugs. *British Medical Journal*, 1998 May 16; 316: 1511-1514.
29. Palaian S, Mishra P, Shankar PR, Dubey AK, Bista D, Almeida R. Safety monitoring of drugs - Where do we stand?. *Kathmandu University Medical Journal*, 2006; 4(1): 119-127.
30. R. Arulmani, S.D. Rajendran & B. Suresh. Adverse drug reaction monitoring in a secondary care hospital in South India. *British Journal of Clinical Pharmacology*, 2007; 65(2): 210-216.
31. Kheirollah Gholami, Gloria Shalviri. Factors Associated with Preventability, Predictability, and Severity of Adverse Drug Reactions. *Annals of Pharmacotherapy*, 1999 February; 33(2): 236-40.
32. P Subish, M Izham, P Mishra. Evaluation of the knowledge, attitude and practices on adverse drug reactions and pharmacovigilance among healthcare professionals in a Nepalese hospital: a preliminary study. *The Internet Journal of Pharmacology*, 2007; 6(1).
33. Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC. Evaluation of patient reporting of adverse drug reactions to the UK Yellow Card Scheme: literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technology Assessment Journal*, 2011 May; 15(20): 1-234.
34. Yellow card reporting scheme: what to report and where to? *Tomorrow's Pharmacist*, p66. URI: 10021494.
35. American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. *American Journal of Health-System Pharmacy*, 1995; 52: 417–9.