ABSTRACT
This article is about the overview of adverse drug reactions and its classification, the causes and steps to prevent adverse drug reactions is also discussed. Adverse drug reaction can be defined as unwanted, unexpected, uncomfortable, or harmful effects that a drug may cause. ADR can be due to Dose-related (overdose toxicity) or non dose related (allergic reaction).Polypharmacy, drug interaction and medication error are the common causes of ADR. There are also the steps taken by the health care professions and the patients in prevention of ADR. International official bodies are also listed in this article together with the reporting forms where the adverse drug reaction in reported and monitored.

KEYWORDS: Adverse drug reaction, causes, prevention, reporting forms, ADR. Significance.

INTRODUCTION
World Health Organization (WHO) defines Adverse Drug Reactions (ARDs) as “Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy.”[1] It is an reaction occurs at the time a drug is used for the purposes of treatment. Adverse reactions to medications are very common, yet everyone responds differently. One person may develop a skin rash, itching or other reactions when taking a certain medication, while another person on the same drug may have no adverse reaction at all.[1] ADRs does not include therapeutic failures, poisoning, accidental or intentional overdoses.[2]
Adverse reactions to medications range from vomiting and hair loss with chemotherapy drug to upset stomach from aspirin or diarrhoea from antibiotics. If patients take Angiotensin Converting Enzyme (ACE) inhibitors drugs for treating high blood pressure, they may develop a cough, facial or tongue swelling. In many cases, it is difficult to determine if the reaction is due to the medication or anonymous reason. This is because the symptoms develop may be similar to other disease conditions. Idiosyncrasy is the term used to classify unexpected adverse reactions that are not dose-related or allergic. Idiosyncrasy is where the abnormal response to a drug and the cause is unknown.

Adverse drug reactions have long time been recognized as a potential unwanted outcome of taking medicines, and the severities of such reactions may vary person to person. Investigators have strived to identify the key factors that increase a person’s risk of suffering ADRs. Patients which taking many drugs, older adults, young children and pregnant women are the higher risk factors for the adverse drug reactions. Adverse drug events cause over thousands emergency department visits each year. Nearly quarter of the patients need to be hospitalized for further treatment after emergency visits for adverse drug reaction as more people take more medicines, the risk of adverse reaction will be greater.

As people gets older much complication arises and they tend to be on more medications. Older adults (65 years or older) are twice more likely as others to get adverse drug reaction and most likely need to be hospitalized. Multiple drug therapy and drug interaction, are frequently reported risk factor for adverse drug reaction, as people increases the number of prescribed drugs with multiple chronic conditions to cure their diseases.

Adverse drug reactions can be classified into six types: dose related (Augmented), non dose related (Bizarre), dose and time related (Chronic), time related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Some adverse drug reactions are very common and can easily predictable. Most adverse drug reactions are relatively mild and short duration. It will be disappearing when the drug is stopped or the dose is changed. Some gradually will reduce as the body adjusts to the drug, while other adverse drug reactions are more serious and last longer.

From the earliest times, pharmaceutical formulations have been recognized as being potentially dangerous to human consumption. Since the Thalidomide incident in 1961 which was the major modern catastrophe, the drug regulatory authorities have been focusing on the
preclinical testing and clinical evaluation of drugs before being marketed to the public. These authorities also increase awareness of adverse reaction, method of detecting and monitoring them.\(^5\)

**Classification of adverse drug reaction**

Adverse drug reactions can be classified into two major groups, Type A and Type B. These reaction known as the Rawlins–Thompson classification. They are also can be divided into four sub-types: Type C, Type D, Type E and Type F.\(^6\) An extended version of this classification system are shown below

**Type A “Augmented” reactions**

- There are expected exaggerations of the drugs known effect. They are usually dose dependent and easily predictable and account for the major cause of adverse drug reaction.\(^7\) These reaction include: higher than normal dose administered, impaired metabolism or excretion, or very sensitive individuals. These reactions are often found in the approved drug product labelling. These reactions are detected earlier in clinical development. For example overdose of insulin can cause hypoglycaemia and excesses use of anticoagulant like heparin, warfarin can cause spontaneous bleeding.

**Type B “Bizarre” reactions**

- There are idiosyncratic or allergic reactions and usually unrelated to the drug's pharmacology of action. Type B reactions are not related to the drug dose, are unpredictable, uncommon, and usually more serious than Type A reaction.\(^6\) Examples are hypersensitivity reactions like Stevens-Johnson’s Syndrome and haemolytic anaemia. These reactions can be known after the drug been marketed over the years.

**Type C “Chronic” reactions**

- This happens due to long term chronic use of a drug. It involves in dose accumulation over period of time during the treatment. It is usually related to the dose and duration of treatment. Example NSAIDs induced nephropathy.

**Type D “Delayed effect” reactions**

- These are found after long term use of a drug. For example effect like teratogenicity and carcinogenicity.\(^5\) Teratogenicity is abnormal congenital malformation of fetus due to use of some drugs during the pregnancy. Carcinogenicity is the ability of the drug to cause cancer or
carcinoma after long term of drug use. Example teratogenicity effect due to thalidomide which is taken for morning sickness symptoms during pregnancy.

**Type E “Ending of drug used” reactions**
- These are the manifested after withdrawal of a drug which was used for a long period of time. Example corticosteroids cause acute adrenal insufficiency; opioids induce narcotic withdrawal and angina pectoris after sudden stop of beta blockers.

**Type F “Failure of efficacy” reactions**
- This is where the recommended drug fail to treat the patient’s medical condition. This may due to the counterfeit of medications, under dosing treatment or disease which resistance to the drug.

**Causes of Adverse drug reaction**

1. **Multiple drug therapy (poly pharmacy)**
   Multiple drug therapy is when the patients is taking more than two drugs for his or her treatment. The likelihood of ADRs occurring may increase as the number of prescribes drug increases. Prescribing drugs like beta blockers, calcium blockers, diuretics drugs which use to treat hypertensive may cause patients to have hypotention or bradycardia.

2. **Drug-drug interaction**
   Certain drugs may cause interaction when they are prescribe together. The risk drug-drug interaction increases with poly pharmacy. For example Theophylline toxicity when given along with erythromycin.

3. **Drug allergic reaction**
   Some patients are allergic to certain drugs. This may due to some genetic factors or heredity. When they take these drugs, allergic reaction like skin rash, itching or flashing may occurs. Example anaphylaxis with penicilin or anaemia by antioxidant drugs.

4. **Drug overdose**
   Drug overdose occurs when the patients taken more than the normal recommended dosing regimen for therapeutic activity. For example overdose of Spironolactone may cause hyperkalaemia that result in irregular heart beat Hepatotoxicity due to Paracetamaol overdose.
5. Poor communication
Poor communication between the health care professional and patients may also lead to adverse drug events. The patients may interpret wrongly when the physician or pharmacists were explaining on their drug therapy.

6. Medication errors
Medication error occurs when an inappropriate use of a drug that may result in harm and such errors may occur during prescribing, dispensing, administering, adherence, or monitoring of a drug. Example of medication errors are wrong drug, wrong routes, wrong patients, wrong time and wrong dose.

Risk Factors for Adverse Drug Reactions
There are several risk factors that can increase the chances of an adverse drug reactions occurrence. They include using several drugs by the patients, an older adult, a young children, breastfeeding and pregnant women.\(^{11}\) Hereditary or genetic factors also cause some people more susceptible to the toxic effects of certain drugs. Certain disease condition may alter the drug pharmacokinetics and pharmacodynamics action, therefore increasing the risk of adverse drug reactions.

■ Use of Several Drugs
• When a person is taking several drugs, whether prescription or over-the-counter medication, it may contribute to the risk of having an adverse drug reaction.\(^{8}\) The risk of adverse drug reactions increase gradually as the number of drugs taken increases. The consumption of alcohol, which is technically a drug, also increases the risk of adverse drug reactions. The patients should consult with the physician or pharmacist on their current medication to make appropriate adjustments that can reduce the risk of an adverse drug reaction.

■ Age
• Children that is very young, these includes infants are at high risk of adverse drug reactions.\(^{9}\) This is due to their capacity to metabolize the drugs is not fully developed well. For example, antibiotic like chloramphenicol cannot metabolize and eliminate by newborns. Newborns that are given the drug may develop gray baby syndrome, which is a serious and fatal reaction. If a drug like tetracycline which is an antibiotic, is given to young children during the period when their teeth are being formed, it may cause a permanent discolour tooth.
enamel. Children who are below 18 years old are higher risk of Reye’s syndrome, if they are prescribe with aspirin while they having influenza or chickenpox.

- Older or aging people are also at high risk of having an adverse drug reaction for several reasons. As they gets older they are likely to have many health issues and thus to be taking several medications to improve their health condition. Besides, as people age, the ability of the liver or kidney to metabolize these drugs becomes less efficient therefore unable to eliminate these drugs from the body. Then these people most probably have greater risk of adverse drug reactions.

- Furthermore, older adults are also more sensitive to certain drugs and its effect. For example, these people are more likely to experience nausea, vomiting, drowsiness, diarrhoea, depression, anxiety, confusion, low blood pressure and impaired coordination when prescribe those drugs. Drugs that can cause these reactions include many sleep aids drugs, anti-histamines, anti-hypertensives, anti-anxiety, anti-depressants and anti-convulsion drugs.

**Pregnancy and Breastfeeding**

- Several drugs are prohibited during the pregnancy period and also while breastfeeding the newborns. This may pose a risk to the health and the foetus development. Anti-hypertensive drugs such as Angiotensin-converting enzyme inhibitors and Angiotensin II receptor blockers. To the extent possible, pregnant women should not take any drugs, especially during the last trimester as the risk is greater during the last trimester of pregnancy. Use of any prescribed drugs, non-prescribed drugs, over-the-counter drugs, or dietary supplements during pregnancy requires a doctor's advised. Alcohol and nicotine smoking also pose high risks to the pregnancy and the foetus.

- Certain medications and traditional herbs may be pass through breast milk to an infant. Certain medication should not be taken by women who are breast feeding. As this drugs may harm the newborns. Certain drugs do not usually harm the breastfeeding infant. However, to be a safer side, women who are breastfeeding must consult with health care professional before taking any medications.

**Prevention of Adverse Drug Reaction**

As we all know that adverse drug reaction can cause serious effect on the patient’s health yet by taking special precaution adverse drug reactions can be prevented. There are few steps that
can be taken to prevent ADRs in significant rate. Below are the role can be played by the health care professional and patients to prevent ADRs.\textsuperscript{[13]}

1. \textbf{Improve the knowledge of the drugs and obtain more information about the patients.}
   - As a health care provider, the physician and pharmacist must have vast knowledge about the drugs action in the body and how the body system response to it.\textsuperscript{[12]} Furthermore, they must able to answer any question been raise by the patient.
   
   - Besides, the health care professional must gather more information about the patient demographic profile, their current and past medical history. Some patients are allergic to certain medications. Ask the patient whether they are allergic to the drugs which been prescribe to them.

2. \textbf{Used computerized system to prevent adverse drug events}
   - Computerized system should be used in hospital setting when prescribing drugs to the patient. By using the system we can prevent any adverse drug event before reaching to the patients.\textsuperscript{[14]} At times it is difficult for a pharmacist to read the drug prescription due to poor handwriting by the doctor. By switching to prescription order entry, we can prevent adverse drug events occurs in the patients.

3. \textbf{Increase communication between health care professionals.}
   - By enhancing communication between health care professionals, they can make better decision what are the best drug treatments for the patients to improve their health condition.

4. \textbf{Pharmaceutical care must be more patient-orientated.}
   - As we all know that a patient comes to hospital with a hope getting cure from their medical condition. As a health care provider, it is their duty to give to patients the best therapy to get cure and improve their lifestyle.\textsuperscript{[12]} For example, the pharmacist role are not only to compound and disperse the drugs but also need to consult the patients about their medications.

5. \textbf{Reduce multiple drug therapy}
   - Patients who are been prescribe more numbers of drugs for treating their diseases are known as poly pharmacy. As the patients been prescribe more drugs, it is more likely the patients risk of adverse drug reactions. The physician must reduce multiple drug therapy and
prescribe a drug which able to treat more than one diseases. By reducing to a few drug, the risk of adverse drug reactions will be reduces.[13]

   • Certain drugs like Digitoxin, Theophyline, Phenitoin and Warfarin having a narrow therapeutic range. A slide increase in dose of these drugs can cause serious toxicity which can be fatal and damage the body systems.

7. Documentation and reporting known adverse drug reactions (ADRs)
   • Documentation and reporting ADRs can prevent further possible damage related to unexpected risk.[17] By reporting these adverse drug reactions to the official bodies, they will investigate and monitor the adverse drug reaction.

8. Patients playing active role in their medications.
   • Patients should make a list of every medication taken with a proper dosage. These include over the counter drugs, herbal supplements and even vitamins. As these may cause adverse reaction too. They should know the indication for the each drug they taken and they can ask the physician how long it take them to cure.[15]

9. Communicate with your health care providers
   • Patients should talk to the health care providers about their drug treatment. Ask the physician or pharmacist how to take the medication, what are the possible side effects and anything related which can improved their health condition. Having a good relationship with your health care providers is important.[15]

10. Take the medication that is prescribed at the prescribed dose
    • Patients should take the drug according what have been prescribe by the physician .Drug which is taken overdose or under dose can be fatal to the patients.

11. Invest in a medication reminder box
    • Patients that are prescribed with more number of drugs should buy a medication reminder box. Patients tend to forget and confuse which drug need to be taken as there are number drugs. By investing in a medication reminder box, the patients able to know which and when the drugs need to be taken for their treatment.
12. Pay attention to side effects and discontinue medications

- Patients should pay attention to a side effect arising from a drug although it is a minor one like skin rashes or light headaches. This could be a sign of an adverse reaction. Patients should discontinue the prescribe if the side effect prolong a long time and should refer back to the doctor or pharmacist.\(^{[14]}\)

13. Don’t take someone else medications

- Each drug is prescribed to the patients according to their age, gender, weight, condition and also other factors. Although the drug belong to the same classification of drug, it may not be suitable for other patients which having the same disease. There are reason why the physician prescribed a particular drug to a patient.\(^{[15]}\)

Monitoring and Reporting of Adverse Drug Reactions

There are many countries has their own official monitoring and reporting the drug safety and reactions.\(^{[16]}\) Documentation and reporting of ADR can be addressed to the available official bodies. At International level, the World Health Organization (WHO) runs the Uppsala Monitoring Centre in Sweden and European Medicines Agency (EMEA) in European Union country. In the United States, they have Food and Drug Administration (FDA) is responsible for detection and monitoring and in Australia, the Therapeutic Goods Administration (TGA).\(^{[17]}\) By reporting the ADR, action will be taken to reduce and prevention ADR. This can prevent drug induced human suffering and also avoid any financial risks associated with ADR. Absent or incomplete documentation of known ADR may cause potentially fatal outcomes. Anybody can report the suspected ADR to these body whether the health care professional or the patients, which is an early alert system.\(^{[16]}\) Only through such reporting can adverse drug reaction can be identified and investigated.

These bodies identify efforts to date, to measure, prevent adverse drug reaction, and promote medication safety. Besides, these agencies was established to identify common, preventable, and measurable adverse drug reactions that may result in significant patient harm and align the efforts of Federal health agencies to reduce and prevent patients harms from these specific adverse drug reaction nationally.\(^{[18]}\) The information and reporting forms about adverse drug reactions are available at the website of these agencies. Example yellow card scheme, Blue card, Medwatch and MedEffect website. Below are the international bodies and reporting
forms where the health care professionals and patients can report any adverse drug reactions incidence.\textsuperscript{[17]}

1. MedWatch runs by the Food and Drug Administration (FDA) in the United States.
2. European Medicines Agency (EMA) runs by the European Union.
3. MedEffect Canada runs by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) in Canada.
4. Australian Adverse Drug Reaction Reporting System runs by the Therapeutic Goods Administration (TGA) in Australia.
5. Yellow Card Scheme runs by the Medicines and Healthcare Products Regulatory Agency (MHRA) in United Kingdom.

\textbf{Figure 1: Example of Adverse Drug Reaction reporting form}
CONCLUSION
An adverse drug reaction is an unwanted effect result by taking a drug. ADRs may occurs following a single dose or prolonged administration of drug or results from taking more than two drugs, adverse drug reactions pose a significant burden on the health system. The public should aware the possible risk of ADR. Spontaneous reporting for those ADRs can be an early warning alert and action will be taken to monitor and investigate.

The severity and incidence of adverse reaction can vary by patient characteristics (age, sex, race, genetic or geographic factors) and also by drug factors (type of drug, dosage, administration route, duration of treatment or bioavailability of drug in the body) Incidence of ADR is probably more higher among the elderly people and taking more number of drugs. Although this may not be the primary cause, the contribution of wrongly prescribing also is the possible incidence of ADR.
REFERENCES


