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RESEARCH ARTICLE

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INTRODUCTION

"Any response to a drug which is noxious, unintended & which occurs at dose normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological functions." It may be leading to cause morbidity & mortality & also affect the quality of life, huge economic burden on the patients. (Srinivasan, R. et al., 2011).

Drug is the chemical entity which is used to treat, cure & prevent or diagnose the diseases or used for the increased the patients well being. It is used to modify or elevate the physiological systems or pathological states for the benefit of patients. But it will also carry some risk of harm i.e., adverse reactions. Drugs are the double edged weapons somewhat it is efficacious or help in the well being of patients & somewhat it produces adverse reactions or side effects which is harmful to the patients. (Phatak, A. et al., 2003) Drug toxicity is the major problem at a global level. It may affect the patient's health as well as the financial burden on the patients.(Sharma, M. et al., 2014) ADRs led to cause a morbidity and mortality in patients. In many countries, ADRs are considered as the 4th to 6th leading cause of death among the hospitalized patients.(Surendiran, A. et al., 2010).

ADR produce a negative impact on both patient well being and health care costs. In India, ADRs monitoring and reporting activity is in its neonates. India is a developing country with the account of 10% of global intake of medicines. It is the fourth largest producer of pharmaceuticals in the world with more than 6,000 licensed drug manufactures and over 60,000 branded formulations. Thus, it is necessary that the drug therapy should be safe, efficacious and cost effective. It is emerging as an important clinical trial hub exposing larger

population to newer drug treatments. It is somewhat necessary to identify adverse drug reactions as soon as possible and to prevent them if possible, tp ensure the well being of the patients at a reasonable costs or to protect the population from the potential harm that may be caused by some of these new drugs. CDSCO (Central Drug Standard Control Organization) has initiated a well structured and highly participative National Pharmacovigilance Program (NPP) was officially inaugurated by the Honorable Health Minister Dr. Anubmani Ramadoss on 23 Nov, 2004 at New Delhi. But this attempt was unsuccessful and hence again from the 1st January 2009, the WHO sponsored and World's Bank funded National Pharmacovigilance Program (NPP).(Hussain, M. M. et al., 2010).

The safety of drug prescribing has become a highly visible topic in medicine, due in part to research suggesting that there are important ADRs caused by commonly used medications. Patient constitute a vulnerable group with regard to rational drug prescribing since many new drugs are increased by day by day into the market without the benefit of even limited experience.(Ramesh, M., 2003) This deficiency causes a practitioner to often prescribe drugs in an "off-label" manner, i.e., increasing the risk of occurrence of ADRs. As more drugs are marketed & as more individuals take multiple drugs, the risk of drug toxicity will probably continue to increase. (Pirmohammed, M. et al., 1998).

Mainly, evaluated the drugs which are more responsible for causing an ADR and the patients population who are at greater risk. In a worldwide, the most commonly a factor which is responsible to cause an ADR is the number of drugs increasing in the market, an aging population and the poly pharmacy.(Digra, K.K. et al.,2015) A study evaluated that 0.7% of admissions in hospital are commonly due to Adverse Drug Reaction; 3.7% of inpatients experienced an ADR, while some serious reactions even lead to be fatal in about 1.3% of patients which are hospitalized.(Pirmohammed, M. et al., 1998; Digra, K.K. et al.,2015; American Society of Health-System Pharmacists,1995).

These are the factors which influenced the incidences of ADRs i.e., age, sex, concurrent disease, genetic factors, drug related factors like type of drug, route of administration, duration of therapy and amount of dose. Others risk factors are increased number of drugs, advanced age, length of hospital stay, gender and function of excreting organs.

Psychoses a mental disorder characterized by a disconnection from reality. Antipsychotics drugs are the most effective drugs which is used in psychiatry in the maintenance therapy of

mania, psychoses and schizophrenia. (Aarsland, D., et al., 1999) Antipsychotics are abundant in numbers and their use is increasing day by day. These drugs causing a number of ADRs & may direct to noncompliance or discontinuation of therapy.(Cooper, C. et al., 2007) Some ADRs may fatal.(Rani, F.A. et al., 2009; Aronson, J.K.et al., 2006; Glassman, A.H.et al., 2001) The incidences of ADR are influenced by patient characteristic such as age, gender. The selection of Drugs should be done on an individual patient basis. The patient involvement is necessary in prescribing decisions and should be discussed about ADRs due to drug by the practitioners.(Haddad, P.M. et al., 2007).

Antipsychotics are most widely used in psychiatric patients. The introduction of 1st generation of antipsychotics drugs prompted large changes in the field of psychiatry, lead to a medical and pharmacological understanding of mental problem. Antipsychotic drugs treatment is very beneficial to the patients followed by the identification of adverse reaction i.e., EPS (Extra Pyramidal Symptoms) particularly at higher hoses.(Bates, D.W. et al., 1997; Serretti, A. et al.,2004; Lublin, H. et al., 2005) Over the last few years, atypical antipsychotics are used in the treatment of schizophrenia. These agents improve quality of life, have better medication compliance and also decrease suicidal tendencies and depression in psychiatry patients. (Gardner, D.M.et al., 2005; Keck, J.P. et al., 2002; Shriqui, C.L. et al., 2001; Bayle, F.J. et al.,2001; Zanarini, M.C. et al., 2001) The second generation of antipsychotic drugs are differ from the first generation as they have low risk of adverse reactions such as EPS and other positive and negative symptoms of schizophrenia. But, the second generation of antipsychotics also have own spectrum of adverse effects including hypotension, seizures, weight gain, diabetes mellitus and hyperlipidemia. Therefore, it is necessary to assess the ADR and achieving a successful treatment. (Shelton, R.C. et al., 2001; Meyer, J.M. et al., 2001; Haupt, D.W. et al., 2001)

1.1 Classification of Antipsychotic Drugs

Antipsychotic drugs are classified into several classes.

I) Phenothoiazines

It is divided into three groups which is different from each other by the side chain of the molecules. Aliphatic side chain & piperidine side chain are less potent than the piperazine.

- Aliphatic side chain: Chlorpromazine, Triflupromazine.
- Piperidine side chain: Thioridazine.
- Piperazine side chain: Trifluoperazine, Fluphenazine.

II) Butyrophenones

In this class of drugs, haloperidol is most widely used drug. It is more potent class of drug. It consists of Haloperidol, Trifluperidol, Penfluridol.

III) Thioxanthenes

It is less potent drugs i.e., Flupenthixol.

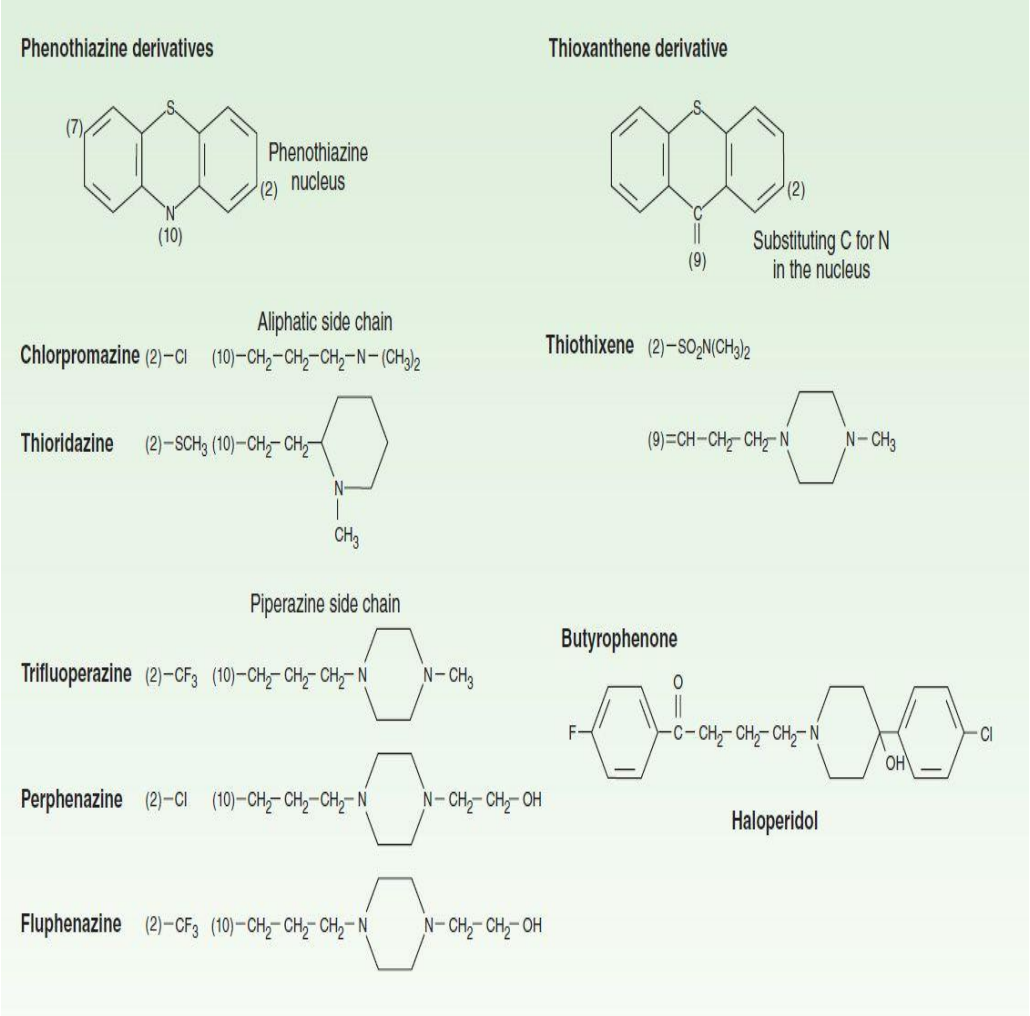

Fig. 1.1: Shows structure of first generation antipsychotic drugs.

IV) Other heterocyclics

These drugs have same efficacy as typical antipsychotics drugs. These agents are Pimozide, Loxapine.

V) Atpical Antipsychotics

Atypical antipsychotics have a broad spectrum of therapeutic effect in clinical practice and they have a less risk of ADR.

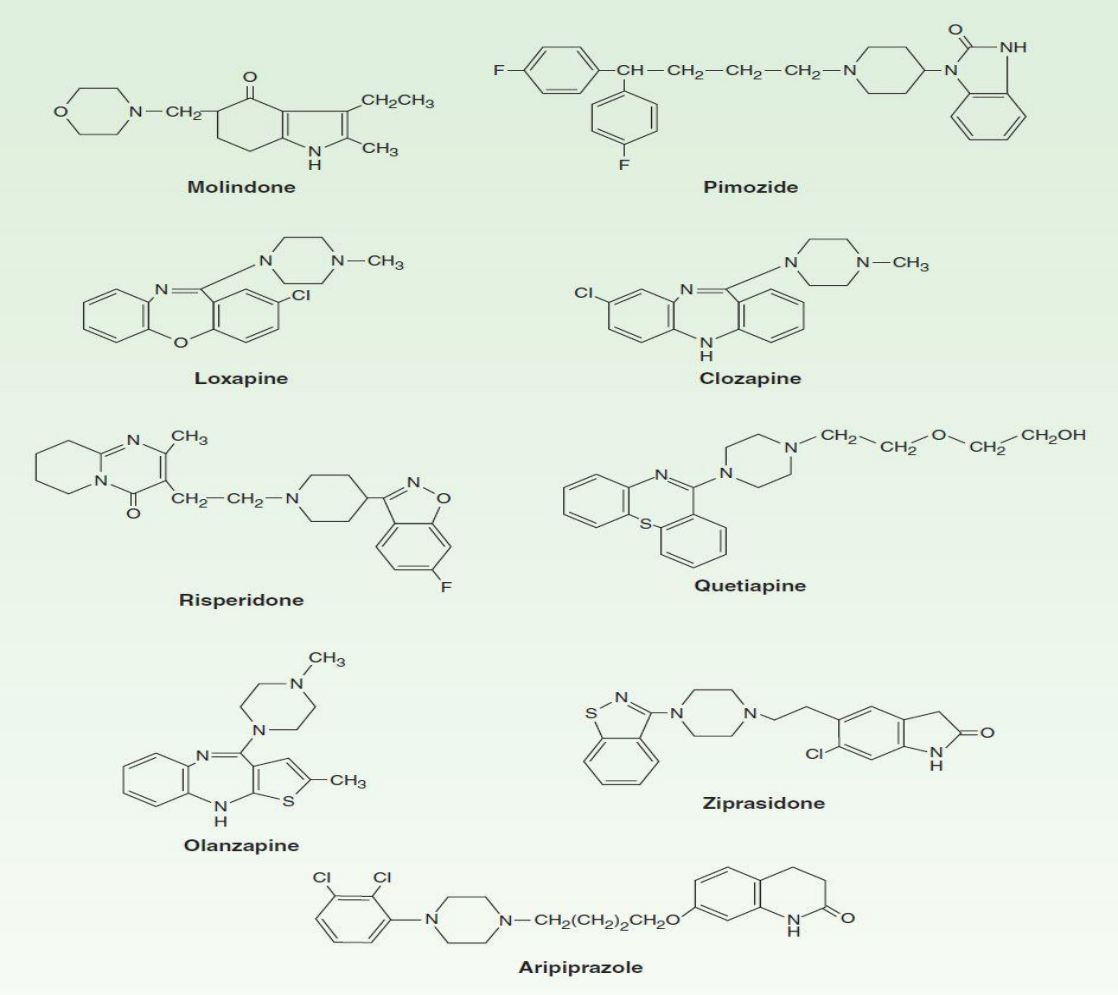

Fig.1.2 Shows structure of second generation antipsychotic drugs.

1.2 Mechanism of action of antipsychotic drugs

Schizophrenia is a chronic mental disorder characterized by positive and negative symptoms such as hallucinations, delusions, thought disorders & social withdrawal as well as cognitive & functional impairment. It affects a person feelings, perceptions, & overall behavior. Antipsychotics drugs are the mainstay of treatment of schizophrenia. Pharmacodynamics property of all antipsychotics is D2 receptor antagonism that has given rise to the hypothesis that schizophrenia & other related disorders involves the dysregulation of dopaminergic circuits with increase dopaminergic activity in mesolimbic pathway which lead to positive symptoms & reduced of dopaminergic activity in mesocortical pathway may lead to negative symptoms. (Howes, O.D. et al., 2014)

The mechanism of action of these drugs is mediated mainly by dopamine neurotransmitter system. Antipsychotics drugs are the cornerstone of the pharmacological treatment such as chlorpromazine which is introduced in 1952 as a first generation antipsychotics drugs.

(Divac, N. et al., 2014) The early antipsychotics drugs are also come in the market as chlorpromazine, haloperidol, fluphenazine are referred to as first generation antipsychotics. These agents are effecting in relieving positive symptoms but also exhibit a extra pyramidal symptoms, tardive dyskinesia i.e., drawbacks of these agents. The drawbacks of these agents may lead to introduced of newer antipsychotics agents in 1990s such as resperidone, olanzepine, quetiapine, etc. Newer antipsychotics are now termed as second generation antipsychotics which have a low tendency of exhibiting a extra pyramidal symptoms & tardive dyskinesia & also have high frequency of producing some adverse reactions such as weight gain, metabolic changes, & associated cardiovascular consequences. (Kuroki, T. et al., 2008).

The first generation antipsychotics are effective in the treatment in schizophrenia but also have tendency to exhibit extra pyramidal symptoms & lead to tardive dyskinesia. However, clozapine withdrawal from the market by manufacturers because it have ability to produce agranulocytosis but, later it is reintroduced in the market with strict regulations as white blood cell count follow up & other investigations. (Kane, J. et al., 1988; Hippius, H. et al., 1989) All the antipsychotics are effective by binding on D2/D3 receptors in the ventral striatum and antagonize its action. (Agid, O. et al., 2007) Both first generation & second generation antipsychotics is associated with a clear, dose-dependent risk of seizure provocation. The risk of seizure provocation is high with first generation antipsychotics drugs as compared to second generation antipsychotics drugs. (Hedges, D. et al., 2003) The majority of adverse effects of antipsychotics agents are extensions of their pharmacological action, also there are some idiosyncratic adverse effects. (Potter, W.Z. et al., 2004) In general, antipsychotics agents have better mainstay in treatment of psychoses & other mental problems but also have tendency to cause adverse effects.

1.3 Pharmacokinetics

Mostly, all the antipsychotics drugs are readily but incompletely absorbed. Many drugs undergo first pass metabolism. The oral administration of Chlorpromazine & Thioridazine have systemic availability of 25-35%, whereas Haloperidol systemic availability of about 65%. Antipsychotic drugs are highly lipid soluble & protein bound i.e., 92 to 99%. They also have a large volume of distribution (i.e., >7L/Kg). They have long duration of action than would be estimated from their plasma half-lives. Symptoms of psychoses will be reoccurrence in 6 months after the discontinuation of treatment.

Antipsychotics drugs are metabolized by the oxidation, demethylation, catalysed by liver microsomal CYP-P450 enzymes, CYP2D6, CYP1A2, CYP3A4. The elimination t1/2 is variable, but mostly is in the range of 18-30 hrs. The metabolites are excreted in urine & bile weeks after the discontinuing of treatment. The broad spectrum of pharmacokinetics of neuroleptics is similar.

1.4 Pharmacovigilance

According to WHO," Pharmacovigilance is the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines.

Pharmakon (Greek) – Drug
Vigila (Latin) – to keep watch

Its main purpose is to reduce the risk of harm to the patients. This idea is come up after thalidomide tragedy in 1961 for introducing the concept of International Drug Monitoring System (IDMS) by the WHO.

1.4.1 Need Of Pharmacovigilance

When a drug comes into the market, there is still a great deal that is unknown about the safety of the product as collected information from clinical trials is in complete with regard to adverse drug reactions, because of

- Preclinical studies are insufficient to predict human safety.
- Patient's safety in clinical trials is limited in number and information of ADR in special group of population is not available.

ADRs are the 4^{th} to 6^{th} largest cause of mortality and morbidity. A response to a medicine used in humans or animals, which is noxious or unintended, including lack of efficacy and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine. Therefore, it is important to permit early detection of less common or serious ADRs and safety problem data. Knowledge of assessment of ADR due to different antipsychotics is necessary. It helps to choose the safe treatment and reduce the risk of occurrence of ADRs by the clinicians. Inadequate knowledge, attitude and practice of reporting and assessment of ADRs are a drawback of our society.

Therefore, Pharmacovigilance help to evaluate the safety profile of drugs. Pharmacists play a vital role by collecting the safety profile data and preserving the safety and quality of life of patients.

India facing the challenges of reporting of ADRs due to inadequate knowledge regarding the drugs and process of ADR such as what to report, how to report, when to report. ADR reporting in India is still in budding and data rate is below 1% as against the worldwide of 5%.

A low reporting ADR occurrence rate at facility may be because of under reported rather than true incidence. It is need to be strengthened the activity of reporting of ADRs. Since clinical diagnosis of ADR is not possible hence, there is a need of proper system to identify and manage ADR and also implement the training among clinician, pharmacists, and nurses for increase the rate of reporting of ADR. Early detection, evaluation and monitoring of ADRs are essential to reduce the risk of occurrence of ADRs and also improve the patient health. Hence, there is a need for an active surveillance system to detect, and monitor the harmful drugs that have entered into the market. Hence, an attempt has been made in this study by assess and monitor ADRs which are caused be antipsychotics drugs to the inpatients in psychiatric ward of a tertiary care hospital.

1.4.2 Pharmacovigilance involves

- Assessing benefits, effectiveness, and risk of medicines and also encourage the safe and effective use of medicines.
- Promote knowledge, understanding and training to health care professionals.
- Improve patient care and safety in relation to use of medicine.
- Detect problems related to the less of medicine.
- Assess the safety of drug therapies especially recently approved drugs.
- Measure the economic impact of ADR prevention as manifested through reduced hospitalization, optimal economical drug use and minimized organization liability.
- Improve public health in relation to use of medicines. (Pharmacovigilance guidelines)

1.4.3 Definitions of the Terminologies

Adverse Drug Event (ADE) – It is any untoward medical occurrence that may present during treatment with a pharmaceutical product during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

Adverse Drug Reactions (ADRs) - It is an unwanted, undesirable effect of medicines that occurs during clinical use and also has casual relationship between drug and its occurrence.

Serious Adverse Drug Reaction – It is any untoward medical occurrence that at any dose results in death or is life-threatening or requires hospitalization prolongation of hospital stay.

Signal – It is the reported information on a possible casual relationship between an adverse reaction and a drug and unknown or incompletely documented previously.

Spontaneous Reporting – refers to a system where by case reports of ADRs are discretionary submitted to national regulatory authority (NRA) by the professionals.

WHO- UMC - refers to WHO collaborating centre- Uppsala Monitoring Centre (UMC) located at Sweden.

National Pharmacovigilance Centre - refers to the Drug Regulatory Authority (DRA).

Pharmacovigilance Centre - refers to either National Pharmacovigilance Centre (NPC) or any Regional Pharmacovigilance Centre (RPC). (Pharmacovigilance gudielines).

Its main purpose to reduce the risk of drug related harm to the patients. This idea is come up after thalidomide tragedy in 1961. Thalidomide drug prescribed for the morning sickness in pregnant women but it causes a congenital disorder in newborns. So, the earlier reporting of suspected ADRs are necessary for elevating the events which are harmful. The Uppsala Monitoring Centre (UMC) in Sweden maintains the International Database of the ADR Reports, India contributes to this monitoring centre in 2004 but unfortunately it was temporarily suspended in 2009. Then this programmed was relaunched as Pharmacovigilance Programme of India, in July 2010. Initially, national coordinating centre was All India Institute of Medical Sciences, New Delhi; then it was shifted to India Pharmacopeia Commission, Ghaziabad. The Pharmacovigilance activity related to ADR monitored under the aegis of Central Drug Standard Control Organization (CDSCO), New Delhi.

1.4.4 Classification of Adverse Drug Reactions – (Rawlins, M.D., 1977; Edwards, I.R. et al., 2000)

I) Rawlins and Thompson desired a convenient method of classifying ADR in 1977. They categorized all ADRs as either Type A or Type B Reactions.

Type A (Augmented)

- Arising from the exaggerated but normal pharmacological action of a drug.
- They are common and predictable.
- Based on pharmacology of the drug.
- Dose dependent reactions.
- Have high morbidity but low mortality.
- Example – bradycardia with β-adreno receptors, hemorrhagic with anticoagulants, atropine induced dry mouth, etc.

Type B (Bizarre)

- Aberrant side effects unrelated to the pharmacology of the drug.
- They are unpredictable and uncommon.
- Have low morbidity but high mortality.
- Example – anaphylaxis due to penicillin, malignant hyperthermia of anesthetic, Johnson syndrome due to carbamazepine, etc.

Limitations of Rawlins and Thompsons Classifications

1. The inclusion criteria for the classification are not clear.
2. Some Adverse reactions do not fit comfortably in this. For Example – cancer patients taking immunosuppressant's reaction at injection sites.
3. In this classification Type B reactions are effectively classed as "everything that is not type A". This renders type B reactions at highly heterogeneous group with little in common, ranging from allergic reactions to extravasations to some forms of Cholestam.
4. Drug interactions involve the interplay between at least two different etiologies to adverse reactions arising from a single chemical entity so they should not therefore be included.
5. Therapeutic failure is not an adverse drug reaction in the traditional sense and cause is often not clear known contributing factors include inappropriate choice of drug, non compliance, under dosage, formulation failure or an idiosyncratic lack of response.
6. According to this classification intentional overdose by the patient causes symptoms described as "toxicity" rather than "adverse effects". But as they arise at doses that are not used clinically and so should be excluded.
7. They state that mortality is likely to be higher with type B reactions that type A. This would not appear to be the case in practice.

8. These classification states that only Type A reaction are dose dependent but Wills et. al, 1999 states that the greater the dose used , the more likely an individual is of to suffer from reaction concerned.

II) Wills & Brown Classification

They proposed a new classification. In this they retain Type A or Type B as such & eight new categories are proposed. And the term 'medicine' has been used in preference to 'drug' to ensure that reactions secondary to the method of administration or exception are clearly incorporated within the definition.

S.NO.	Classification of ADRs	Features	Examples
1	Type A (Augmented)	- They are common & predictable. - Based on pharmacology of drug. - Dose related. - Improves if medicine is withdrawn.	- Hypoglycemia with sulphonylureas. - Bradycardia with β-Blockers, etc.
2	Type B (Bugs)	- Pharmacologically predictable. - Involves interaction with a micro-organism. - Improve if medicine withdrawn.	- Dental caries with sugar coated tablets. - Antibiotics causing overgrowth of resistant bacterial species in intestine.
3	Type C (Chemical)	- An irritant reaction depending on the chemical nature of a drug or excipient. - Related to drug concentration.	- Pain at the site of injection.
4	Type D (Delayed)	- caused by method of administration or nature of formulation. - Improves if medicine withdrawn or method of delivery changed. - Not dependent on chemical or pharmacological properties of drug or excipients.	- Infection at the site of injection. - cough after use drug powder inhaler.
5	Type E (Exit)	- Pharmacologically predictable. - Begins only when medicine stopped or dose reduced. - Improves if medicine reintroduced.	- Withdrawal reaction due to opioids, clonidine, benzodiazepines, β-blockers, etc.
6	Type F (Familial)	- Only occurs in those	- Patients with glucose-

		genetically predisposed. - Improves if medicine withdrawn.	6- phosphate Dehydrogenates deficiency may experience haemolysis when exposed to quinine.
7	Type G (Genotoxicity)	- Causes irreversible genetic damage.	- Teratogenic agent's damage genetic material within the fetus.
8	Type H (Hypersensitivity)	- Requires activation of immune system. - These are most common after Type A reactions. - Improves if medicine withdrawn.	- Allergic skin rashes with antimicrobial agents. - Anaphylaxis with penicillin. - Johnson syndrome due to Carbamazepine.
9	Type U (Unclassified)	- Unknown mechanism of occurrence.	- Drug induced taste disturbance, muscular adverse effects of simuvastatin. - Nausea & vomiting with gaseous anesthetic, etc.

III) Classification of ADR according to WHO 2014

Type A (Augmented) Reaction – These reactions occurs due to exaggeration of normal pharmacological actions of the drug which are when administered at used therapeutic dose. The reactions are usually dose dependent. And also include the reactions that are not directly related to the desire pharmacological reactions. For Ex – Dry mouth with tricyclic antidepressants.

Type B (Bizarre) Reactions – These reactions are novel responses which occur unexpectedly by the drug from its known pharmacological actions. These reactions are rare or might be discovered for the first time even when thew drug is available in the market for long duration for general use. For Ex – Malignant Hyperthermia with general anesthetics.

Type C (Continuing) Reactions – These reactions remain for a long time. For Example – Oesteonecrosis of the jaw with biphosphonates.

Type D (Delayed) Reactions – These reactions appear after a little time when the drug has been used, leading in difficulty in detection. For Example – Leucopenia which can occur up to six weeks after a dose of lomustine.

Type E (End of use) Reactions – These reactions occurs when the drug has been withdrawn. For Example – Insomnia, anxiety which occurs after benzodiazepines are withdrawn.

Type F (Failure) – It occurs due to the insufficient treatment. For Example – Resistance occur due to antimicrobials agents.

1.4.5 Etiology

ADRs have a considerable negative impact in both patient health and health care costs. In India, ADR detecting & reporting activities in its neonates. India is a developing country with the account of 10% of global intake of medicines. It is the fourth largest producer of pharmaceuticals in the world with more than 6,000 licensed drugs, manufactures & over 60,000 branded formulations. Thus, it is necessary that the drug therapy should be safe, efficacious & cost effective. It is emerging as an important clinical trial hub exposing larger population to newer drug treatments. It is somewhat necessary to identify adverse drug reactions as soon as possible & to prevent them if possible, to ensure the well being of the patient at a reasonable cost or to protect the population from the potential harm that may be caused by some of these new drugs. Central Drug Standard Control Organization (CDSCO) has initiated a well structured and highly participative National Pharmacovigilance Program (NPP). (Hussain, M.M. et al., 2010)

In Geriatrics, prescribed drugs have a common cause of ADR. In a study, it was found that the prevalence of ADR related hospital admissions was 5.9%(Harugeri, A. et al., 2011) while in another such study in India, it was observed to be 6.7%.(Malhotra, S. et al., 2001)

Polypharmacy & Self Medication are among the few factors which changes the drug safety by causing drug-drug interaction. Thus, in such cases patient history, drug related information, cause should be properly reported.

Most of the time, drug-drug interaction may also be responsible for causing an ADR which is usually evaluated among the geriatric patients. Drug interaction may cause alteration of drug bioavailability, distribution, clearance & agonistic & antagonistic pharmacodynamics effects.

1.4.6 Diagnosis of ADR – (Pharmacovigilance guidelines)

Diagnosis of ADR is difficult as they are misinterpreted by occurring disease. But in case of drugs that produce specific symptoms help to evaluate a ADR easier as example extra pyramidal symptoms.

A study by Irey explained how to diagnose an adverse drug reaction. Thus, practitioners should follow the aspects before diagnose an adverse reaction.

1. A temporary relationship between drug & occurrence of reaction must be obtained.
2. Diagnosis can be made by a different outlook eliminating the cause other than the suspected drug.
3. Selection of drug which would be suspected to cause ADRs.
4. Dechallenging & rechallenging of ADR must be evaluated.

1.4.7 Factors animate Adverse Drug Reaction

Drug-Drug Interactions – It is also play a vital role for causing an ADR. It is divided into three categories- (Novotony, J. et al., 1999)

1. Pharmacokinetic Interactions.
2. Pharmacodynamic Interactions.
3. Pharmaceutical Interactions.
4. Pharmacokinetic Interactions – When one drug interferes or changes the absorption, distribution, metabolism and elimination of another drug which may lead to alteration of response.

- Absorption – The reactive rate of drug absorption is increased or decreased by the presence of other drug. If, the therapeutic concentration of drug is not reach therefore, the failure of treatment occurs.
- Distribution – Protein binding & cellular distribution reaction are the two type of distribution reaction. Prescribing of administration of two protein binding drug leads to a competitive binding reactions which increases free fraction of other drug.
- Metabolism – Metabolism of other drug leads to cause shortened plasma half lives of other drugs due to microsomes.
- Elimination – Change in Glomerular filtration rate, tubular secretion or urine pH may alter the elimination or excretion of some drugs.

I) Pharmacodynamic Interaction

- Synergistic or Additive Therapeutic effects – When two drugs having similar pharmacotherapeutic actions are administered they produce synergistic effect.
- Antagonistic effect – When two drugs having different pharmacological effects are administered this cause reversing the effect of one of the drug.
- Indirect effect – It occurs when one drug indirectly affect the response of other drug.

II) Pharmaceutical Interaction

i) Drug – Food Interaction – In such interactions the presence of food modifies the activity of drug or any nutritional food. Most commonly in presence of food the absorption of drug is compromised either by delaying or reducing drug's absorption. For Example – Food interferes with absorption of ampicillin, but a fatty meal enhances absorption of griseofulvin & lumefantrine.

ii) Age –Ability of liver to metabolize drug is considered to be low at young old age. Renal function also decreases with increase in age.

iii) Gender – Subjective effects of drugs may differ in female because of their mental makeup. Some drugs cause side effects in men but not in women & vice – versa. Digoxin is reported to be associated with higher mortality among women than among men. Ketoconazole cause loss of libido can only occur in men.

iv) Genetics – Idiosyncratic reactions occur towards a drug due to an abnormal susceptibility of patients. Such types of reaction occur to patients who are genetically abnormal. For example - Doxyrubicin, methylene blue, nalidixic acid, etc.

v) Pregnancy – These are marked & progressive physiological changes during pregnancy which can alter drug disposition. (Galbally, M. et al.,2014)

vi) Gastrointestinal motility is reduced which leads to delayed absorption of orally administered drugs. Plasma & extracellular fluid volume expands – volume of drug distribution may increase & so on. For example – The risk of antipsychotics occur at the time of pregnancy which can lead to prematurity, low & high birth weight & gestational diabetes.

vii) Route of Administration – It may governs the speed & intensity drug response such as Magnesium Sulfate given orally causes purgation, applied on sprained joints – decreases swelling, while intravenously it produces CNS depression & hypotension.

viii) Time of Administration – Hypnotics taken at night & in quiet, familiar surroundings may work more easily while corticosteroids taken as a single morning dose cause less pituitary-adrenal suppression.

ix) Psychological Factors – The effect of a drug relates to a patient's beliefs, attitudes & expectations.

x) Pathological states – Not only drugs modify disease processes, several diseases can influence drug disposition & drug action.

- G.I Diseases – It can alter absorption of orally administered drugs. It may increases or decreases the absorption.

- Liver Disease – It can influence drug disposition by serum albumin is reduced which may reduced the protein binding of acidic drugs & metabolism & elimination of some drugs.
- Kidney Disease – It may affects pharmacokinetics of many drugs as well as alters the effects of some drugs. For Example – The permeability of blood brain barrier is increased in renal failure, NSAIDs cause more fluid retention.

1.4.8 Reporting of ADRs

How to Recognize ADR in patients?

ADRs are difficult & sometimes impossible to find out from the disease being treated since they may act through the same physiological & pathological pathways. However, these are the points which is helpful for proceed towards assessing possible drug – related ADRs.

- To be ensure that the prescribed medicine taken by the patients at the dose advised.
- Take a proper patient's treatment history & does proper examination.
- Establish a temporal relationship when the drug is being exposed & the suspected ADR is started, also the pharmacological characteristics of suspected drug should also be conserved.
- Carry out a through physical examination with appropriate laboratory investigation if necessary.
- Effect of Dechallenge & Rechallenge should be determined.

These are the following points which are also focused for the evaluation of suspected ADRs.

1. If the events is not documented anywhere, it does not mean that it cannot be caused by the suspected drug.
2. When ADR is caused due to drug interaction a relationship with the introduction or withdrawal of interacting drug should be importantly considered in causality assessment.

Who should report ADRs?

Health care practitioners, nurses, pharmacists, & other health workers can play a vital role for reporting of ADRs.

What to report?

- All ADRs of medicinal products either included in the essential medicines list or available in the market in pharmacies.
- All serious reactions & interactions.

- ADRs which are not labeled in the package insert.

How, What & Where to Report?

An ADR Form is obtained by contacting the DRA or Pharmacovigilance centers or DRA webpage. The ADR form should be completely fill as much detail as possible & returned to DRA or any pharmaceutical centers.

Following are the sections which is important to fill in ADR Form:

I) An Identifiable Patient
- Patient Initials
- Sex
- Weight
- Age at time of reaction or date of birth

II) Suspected Medicine
- Name of Drug (Generic & Brand Name)
- Strength (Concentration)
- Dose, Frequency
- Dosage Form
- Route of Administration
- Indication for use
- Duration of use, date started, date stopped
- Batch number

III) Suspected Adverse Reaction
- Description of the reaction
- Seriousness of the reaction
- Date the reaction started, stopped
- Treatment provided for the reaction
- Relevant tests/ Laboratory Data(if available)

IV) An Identifiable Reporter
- Name of Reporter
- Address
- Contact Details
- Qualification (if health care practitioners)

When the reporters or any health care practitioner evaluate or report the ADRs at that time, negative consequences toward reporting come out in the mind of reporter as Will reporting have any negative impact on reporter? Hence, it is clear that no negative impact occur on reporters work.

The outcome of report, together with any relevant informant relating to ADR will be communicated to reporter as appropriate. The details of report stored in a database at DRA & analyzed report will be sent to Uppsala Monitoring Centre (UMC), Sweden.

These are the principles of efficient reporting as in-time reporting i.e., Report the suspected ADRs as much as it is possible. The reports have more accurate data about suspected ADR, then, send to the report quickly to any Pharmacovigilance centre or DRA. Also keep vigilance for signs & symptoms that may increase or exclude the possibility of a medicine induced reaction. All follow up information should be submitted to Pharmacovigilance centre by "FOLLOW UP REPORT" i.e., updated in the right corner of the form. Form is filled with accuracy and all the relevant information. This is also essential for assessing the causality of the medicine to have caused that ADR. After filling the ADR form with all relevant information will be uploaded on the database. Then, the reported case will be entered into the National level & analyzed by expert reviewers. Therefore, the purpose of ADR reporting is fulfilled by reducing the risk of harm caused by the medicine prescribe and administered & also improve the patient care & safety.

1.4.9 Analyzed & Causality Assessment of ADRs

It is the method by which the causal relationship is established between a medicine & a suspected ADRs. Causality Assessment is done by several methods i.e., Naranjo ADR Probability Scale, French Imputation System, Bayer's Theorem, WHO Causality Categories & so on. But, the most common method which is used to assess the causality of ADR i.e., Naranjo's Scale & WHO Scale of assessment. It is use for improve the scientific basis of assessment, mark individuals case reports, classify uncertainty. But, it has some limitation in change uncertainty to certainty, distinguish valid from invalid cases & so on.

I) WHO-UMC Causality Assessment System

i) Certain: A Clinical events, including laboratory test abnormality, which occurs in a plausible time relationship to medicine administration & which can't be explained by concurrent disease or other medicines or chemicals. Dechallenge should be clinically

plausible. The events must be definitive phenomenologically, i.e., an objective & specific medical disorder or a recognized pharmacological phenomenon). If necessary, a rechallenge is satisfactory.

ii) Probable/ Likely: A Clinical events, including laboratory test abnormality, with a reasonable time sequence to administration of the medicine, unlikely to be attributed to concurrent disease or other medicines or chemicals, & which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

iii) Possible: A Clinical events, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other medicine or chemicals. Information on medicine withdrawal may be lacking or unclear.

iv) Unlikely: A Clinical events, including laboratory test abnormality, with a temporal relationship to medicine administration which makes a causal relationship improbable, & other medicines, chemicals or underlying disease provide plausible explanation.

v) Conditional/ Unclassified: A Clinical events, including laboratory test abnormality. More data needed for proper assessment or the additional data are under examination.

vi) Unassessable/ Unclassified: Report suggesting for reporting an adverse reaction. It can't be judged by insufficient or contradictory information. Data can't be supplemented or verified. (WHO-UMC, 2014)

II) Naranjo's Algorithm – (Naranjo, C.A. et al.,1981)

It is also named as Naranjo Scale or Naranjo Nomogram. It designed by Naranjo et.al., for determining the possibility of whether an ADR is occur due to drug rather than the other factors. Possibility is considered via a score termed as definitive, probable, possible or doubtful. The author's conclusions are to verifying by the value obtained from algorithm.

Questionnaire –

i) Are there previous conclusive reports on this reaction?

Yes (+1) No (0) Do not know (0)

ii) Did the adverse events appear after the suspected drug was given?

Yes (+2) No (-1) Do not know (0)

iii) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

Yes (+1) No (0) Do not know (0)

iv) Did the adverse reaction appear when the drug was readministered?

Yes (+2) No (-1) Do not know (0)

v) Are there alternative causes that could have caused the reaction?

Yes (-1) No (+2) Do not know (0)

vi) Did the reaction reappear when a placebo was given?

Yes (-1) No (+1) Do not know (0)

vii) Was the drug detected in any body fluid in toxic concentrations?

Yes (+1) No (0) Do not know (0)

viii) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?

Yes (+1) No (0) Do not know (0)

ix) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?

Yes (+1) No (0) Do not know (0)

x) Was the adverse event confirmed by any objective evidence?

Yes (+1) No (0) Do not know (0)

Scoring

- ≥ 9 = definite ADR
- 5 - 8 = probable ADR
- 1 – 4 = possible ADR
- 0 = doubtful ADR

2. REVIEW OF LITERATURE

Gulrez, G. et al., 2018: In this study, the pattern of ADRs was monitoring. 300 patients were reported with the incidences of ADRs. They reported that the occurrence of ADRs due to a drug was more in males than the females. For causality assessment, the WHO Scale was used. They concluded that antimicrobials agents cause more ADRs & the most common affected organ system was skin. According to the casuality assessment, majority of cases of ADRs were probable.

Prajapati, K. et al., 2018: In this study, various characteristics of suspected ADRs were evaluated such as clinical presentation, causality, severity & preventability occurring in hospital. 2977 ADRs were reported out of which 375 were serious. The occurrence rate of ADRs were 12.6%. Skin & Appendages followed by liver & biliary system disorders were the most common affected system. Antitubercular, antiretroviral agents cause more ADRs. Causality Assessment data were rated as possible (182, 48.8%) followed by probable (173,46.1%).

Sharma, R. et al., 2018: This study evaluated the drug which causes ADRs & signs & symptoms of ADRs in a tertiary care hospital. A prospective study was conducted in the hospital at a interval of 1 years. Patients of 60 years & above were included in this study. A total of 1000 prescriptions were analyzed out of which 800(7.1%) ADRs were reported. Out of 800 ADRs, 300ADRs were associated in the elderly patients. Antibacterial agents were the most affected agents who cause majority of ADRs i.e., 19.33% & the most affected system was gastrointestinal tract. They concluded that the occurrence of ADRs due to a drug more in elderly patients. So, the prescriptions given to the patients according to their age.

Biyabani, S.A. et al., 2018: A study carried out on monitoring of ADRs due to antibiotics in a general medicine department that was a prospective observational study for duration of 6 months. Information of ADR was observed by Standard pro-forma. They recorded 100 ADRs from the 100 patients. Majority of cases of ADRs were reported in females than the males. Majority of patients in this study belonged to 40-80 years age group. They found that the GIT (22%) & the skin (19%) were the most affected organ system due to ADRs of Antibiotics. Cephalosporin was the most administered drug followed by others. On the basis of severity assessment mostly reactions were moderate followed by mild & severe reaction. A causality assessment exhibit that 30% were definitely preventable & other reaction were probable & possible. The ADRs can be prevented by collecting reliable information as soon as possible.

Nisa, Z.U. et al., 2018: In this study, the knowledge, attitude & practice of ADR reporting by the health care professionals in a hospital were monitoring. A total of 27 questions were included in the questionnaire & asked from the pharmacists, & health care practitioners. Questionnaire comprises of 12 questions of knowledge, 4 questions of attitude & 9 questions of practice & rest of 2 questions from factors influencing ADR Reporting. The rate of Response is 95.5% among the 384 physicians. They accounted that 83.1% poor ADR reporting knowledge, 78.2% have positive attitude toward reporting of an ADR & only

12.3% hospital had good ADR Reporting practice. They concluded that the reason of poor knowledge, attitude toward reporting of ADRs was lack of knowledge regarding where & how to report ADRs. So, the workshops, trainings & conferences were conducted all over the world wide for providing the proper knowledge about reporting of a ADRs & how much extent it is necessary.

Vishwe, A. et al., 2017: A study to analyze the knowledge, attitude, practice of doctors & nursing staffs toward Pharmacovigilance in a tertiary care teaching hospital in Central India that was a cross-sectional questionnaire based study. A total of 200 health care practitioners take part in this study out of which 150 were resident doctors & 50 were nurses. Questionnaire evaluates the data about knowledge, practice & attitude & then suggestions part also included in this study for improving the ADR Reporting. They found that 82.6% (95% CI 0.7576 to 0.8794) of doctors & 74% (95% CI 0.6033 to 0.8424) of nurses had knowledge about Pharmacovigilance. There was no more difference between knowledge of health care professionals i.e., doctors & nurses (p value is 0.7967). 85% of resident doctors & 80% of nurses give suggestions for conducting training & awareness programme. They concluded health care practitioners were aware about Pharmacovigilance but routine practice of reporting ADR was lacking.

Adhikari, A. et al., 2017: This study was carried out in a tertiary care hospital of Kolkata, West Bengal for the evaluation of prevalence of ADR. It was an observational study & 529 prescriptions were observed out of which 287 patients were suspected from ADRs. Casuality Assessment & severity were determined by the Naranjo's Algorithm Scale & Hartwig Seigel Scale. Naranjo's Scale exhibit that 5% ADR were definite, 40% probable & 55% possible were obtained. They concluded that most of the ADRs caused by the Antihypertensive drugs i.e., 63.07%.

Lucca, J.M. et al., 2017: They studied the cost associated with reported ADRs in which 494 ADRs were recorded among patients. They concluded that 3.44% ADR lead to hospital admissions and 2.83% prolong the hospital stay. CNS and Gastrointestinal systems are the most common symptoms organ class affected by ADRs. The total cost incurred management of 131 ADRs was Rs. 57,891.33.

Prasad, R.J. et al., 2017: A study was conducted in a tertiary care hospital that was a observational study over a period of 6 months to find out the incidence of ADRs in a patients

to different genders. An assessment of causality of ADRs was done using WHO-UMC Causality Assessment Scale & Modified Hartwig Seigel Scale. A total of 30 ADRs Reports were observed i.e., 21 reports(70%) were female & 9 reports (30%) were male. Most of ADRs were probable 20(70%) while 10(30%) were certain. In female, incidences of ADRs were due to many drugs such as antibiotics 15(76.43%), followed by NSAIDs 2(9.52%),& the remaining were due to PPI 2(9.52%) & anticonvulsants 2(9.52%). In males, ADRs were due to 5(55.5%) antibiotics followed by NSAIDs 2(22.22%), & anticonvulsants 2(22.22%). They concluded that the incidences of ADR were higher in females than males.

Paudel, S. et al., 2017: They studied the evaluation of ADRs due to antihypertensive agents in a tertiary care hospital in a Nepal. A total of 382 patients were analyzed, out of which 219 were males & 163 females. 67 ADRs were reported. They classified patients who take antihypertensive agents according to their such as 51 to 60 years were 115 followed by 61 to 70 years were 88 & 41 to 50 years 68. They reported that the Calcium Channel blocker cause more ADRs (i.e., 22 or 32.84%) which was followed by Angiotensin Converting Enzyme Inhibitors (i.e., 17 or 25.38%), Angiotensin receptors blockers (i.e., 12 or 17.91%), diuretics (i.e., 10 or 14.92%), & β- Adrenergic antagonist (i.e., 6 or 8.91%). The most affected system was CVS (40 or 59.7%) followed by CNS (16 or 25.88%), respiratory (11 or 16.42%), dermatological system (11 or 16.42%). According to the Naranjo Scale, definite relationship was established in 9(13.4%) patients while possible in 39(58.2%), probable in 16(23.9%) & 3(4.5%) were categorized as doubtful.

Karen, D.H. et al., 2016: They studied the plan of ADRs among hospitalized patients in psychiatry department. Details were documented in ADR Reporting Form and Causality Assessment was done by Naranjo's Scale. A total of 53 ADRs were recorded. Polypharmacy was seen in 39% of patients who developed ADR. All ADR were observed probable except one is possible.

Darji, N.H. et al., 2016: They studied the incidences of ADRs due to a drug & also evaluate the causality, severity, frequency, type, preventability of ADRs. I was a prospective observational study carried out in a department of general medicine at the duration of 12 month. They included those patients who were admitted due to an ADRs & prolong hospitalization. Total of 101 ADRs were recorded from the 3566 patients. The causality assessment observed ADRs as per WHO Scale & Naranjo Scale through which the most common category was probable in Group A (54.7%) & Group B (50%) & in Group A

(89.9%) & in Group B (84.6%) respectively. The severity was done by the Hartwig Seigel Scale as 65.4% ADR in Group A & 73.1% in Group B were moderate. They concluded that prolong hospitalization, polypharmacy were the most commonly responsible for the occurrence of ADRs & the incidences reported as 2.44%.

Belgadu, S. et al., 2016: They evaluate the incidence & nature of ADRs. It is a retrospective study & can be done by using Chi- Square Test and Student's t-test. The result is incidence of ADR was found to be 10.2%. Weight gain was the most common ADR reported and atypical antipsychotics were most common class of drugs implicated ADR.

Munoli, S. et al., 2016: They monitor the ADR of Antipsychotics and mood stabilizers in psychiatric department. The data was collected in standard questionnaire format. The total of 45 ADRs was recorded and extra pyramidal symptoms, weight gain were the most common ADRs. The most common drugs which cause more ADRs such as Olanzapine, Chlorpromazine. The ADR showed possible to probable and mild to moderately severe respectively.

Afkat, A. et al., 2016: They find out the prevalence and severity of adverse drug reaction (ADRs) in patients subject to different anti-psychotic drugs in a psychiatric department, a study was conducted that was observational study over a period of one year in the outpatient department. An assessment of severity was done using modified Hartwig and Seigel Scale. A total of 100 ADRs of different types were observed in 77 patients out of total 177 patients included in the study, with an overall prevalence of about 43.6%. Most (83.0%) of the ADRs were mild in severity while ADRs moderate in severity were found in only 17(17.0%) according to modified Hartwig and Seigel Scale. None of the reported ADRs belonged to 'severe' or 'lethal' category. There was no statistically relationship between development of ADRs with age (p=0.8) or sex (p=0.6) of the patients involved in the study. Although with utilization of antipsychotics, the prevalence of ADRs in the study was at high 43.6%, most of them (83%) were mild in nature and only 17% of them were of moderate severity and none of our patients showed the development of any severe ADRs which would have lead them to discontinue the therapy.

Nivya, K. et al., 2015: A study review the various drug related problems articles & conducted in th duration of October 2007 to October 2012. Various articles related to drug related problems were reviewed & collected from the pubMed Database. Studies identified DRP

frequency, incidence, risk factors, and trends of DRP hospital admissions. It was concluded that the cost of management were highly effect the severity of reaction and the main factors which were responsible for the DRPs s polypharmacy, polyphysicians, non-compliance, prescription errors. The most common agent which contributed in DRPs were antineoplastic agents, CVS Drugs & CNS Drugs. It also found that the clinical pharmacists play a vital role for prevalence of DRPs.

Farhat S. et al., 2015: They monitored the adverse drug reaction due to antipsychotic drugs among patients attending outpatient department. They found result by the help of questionarrie and the assessment of causality was done using both Naranjo's Scale and WHO-UMC Monitoring Scale. They studied in 177 patients in which 77 patients were suffering from ADRs of 33 different types. Most of the ADRs had a probable.

Kurmi, P. et al., 2016: They studied the pattern of adverse drug reactions of Antipsychotic Drugs in a tertiary care hospital by recording various types of adverse drug reactions related to antipsychotic drugs and finding out the causality, severity and preventability of adverse drug reactions related to antipsychotic drugs. The study was carried out as open label study for a period of six months after getting approval by human ethical committee. During the study, total 359 patients were screened, out of which 197 were males and 162 were females. Out of 359 patients, 33 patients (9.19%) were detected with 12 types of ADRs. Incidence of ADRs was higher in males (22 patients; 66.67%) than females (11 patients; 33.33%). 12 different types of ADRs were detected among which tremor (36.36%) was commonest. Out of 8 antipsychotic drugs causing ADRs, olanzepine (12.8%) was commonest followed by clozapine. Majority of ADRs were assessed as probable (84.85%) according to WHO-UMCcausality assessment system. Most of the ADRs were assessed as not preventable (57.58%) according Shumock and Thronton Scale. Majority of ADRs were assessed as moderate (57.57%) and rest were mild (42.43%) according to Hartwig's severity assessment scale. In this study it was found that tremor was the commonest ADR detected and Olanzepine was the commonest drug causing ADRs.

Shah, V.M. et al., 2014: Their study was based on the evaluation of the incidence in psychiatry ADRs on the basis of observational study. They found among patients in numbers, 28 were sufferings with atleast one ADRs, out of which 12(48.45%) were probable and 12(48.45%) were possible and in total 43 ADRs caused by Amitriptyline and Duloxetine was highest.

Joel, J.J. et al., 2014: Their study based on moniotoring of ADRs on Antipsychotropic drugs in patients who were suffering from Schizophrenia. Data was collected from 200 patients, who were the age of 18 years were included in this study, they find out the result of ADRs caused by the drug in descending order such as Olanzepine (30.16%), Risperidone (29.26%), Clonzapine (20.45%), Amisulpride (4.26%). Mostly, atypical antipsychotics caused ADRs in 40.1% patients.

Lakshmi, P. et. al., 2014: Their study on Adverse Drug Reactions of Antipsychotic in psychiatric patients in a tertiary care hospital was conducted. The study included patients of both sex, prescribed with atleast one antipsychotic and were on polypharmacy. It was a prospective observational study. The medication charts of the patients were analyzed for adverse drug reactions. The causality was assessed by using WHO probability Scale and Naranjo Scale. The severity was assessed using Hatrwig and Seigel Scale. Prescriptions of 200 patients 951% males and 49% females: mean age 24±15.58 years) were studied. 263 ADRs were observed in 158 patients. According to WHO Scale, 87(36.5%) ADRs were found to be probable, 174(63.49%) were possible, 2(0.76%) were unlikely and with Naranjo scale, 96(36.5%) were assessed to be probable, 167(63.49%) were possible. Severity assessment showed that 167(63.49%) ADRs were mild, 96(36.5%) were moderate and there were no severe reactions. The offending drugs were withdrawn and the dose was altered for 32(16%) patients. The study identified participation on the multidisciplinary team can improve the treatment to hospitalized patients and promote drug safety.

Galbally, M. et al., 2014: Their study were reviewed the maternal and fetal effects of antipsychotics drugs on pregnancy. Accordingly, despite antipsychotics being amongst the earliest of psychotropic medications to be introduced, the evidence for their effects secondary to pregnancy exposure is extremely limited. While this review does not identify clear evidence for a risk of malformation, there is evidence for risks associated with pregnancy and neonatal outcomes. Studies identified found risks that included prematurity, low and high birth weight, and gestational diabetes. There have also been studies that suggest neonatal withdrawal and abnormal muscle movements. The longer term neurodevelopmental outcomes for children exposed in utero remain unclear with only four studies identified: two of first generation antipsychotics and two of second generation antipsychotics. When considering the risks of these medications in pregnancy, the risk of untreated maternal illness (particularly schizophrenia and bipolar disorder) on both maternal and child outcomes is

relevant. Future research needs to focus on prospective, longitudinal studies with adequate measures of key confounding variables including maternal mental illness, other exposures (such as smoking, alcohol and illicit drug use) adequate length of follow up where accurate child developmental measures are obtained.

Saramurthy, S. et al., 2014: They analyzed the drug usage pattern of anti-psychiatrics and the common adverse effects provoked by them were designed by some researchers. They included 50 patients in their study who were on the treatment with anti-psychotic drugs. They carried out the study in a specialized psychiatric hospital. The patients were segregated on the basis of age, gender, social history, disease diagnosis and drug usage pattern and common adverse effects of anti-psychiatric drugs observed. Chlorpromazine was found to be the most commonly used drug (62%) followed by Olanzepine (50%). Weight gain was found to be the commonly induced adverse effect of anti-psychiatrics (52%) followed by tremors (50%). Better insight and knowledge of the common adverse effects of anti-psychiatric drugs woulod decrease the incidence of adverse effects. This would eventually increase patient adherence and would enhance therapeutic outcomes.

Hemlata, V.E. et al., 2014: They studied the ADRs of antipsychotic drugs in patients of psychiatric illness was carried that was longitudinal prospective observational study. Information of ADRs was data based and collected from OPD. The noted ADRs were assessed by using Naranjo probability assessment scale, and WHO (UMC) causality assessment scale. They recorded 104 ADRs due to atypical antipsychotics. Majority of patients in this study belonged to 21-30 years age group which was 24% of the total. According to the severity of ADRs, majority of cases were reported of having weight gain 38.46% followed by sedation 19.23%, dry mouth 13.46% and orthostatic hypotension 5.76%. 88.47% were reported as type A and 11.53% were reported as type B. Definite (certain) relationship was established in 30.40% patients while probable in 57.62% and 11.53% ADRs were categorized as possible. The ADRs can be prevented by collecting reliable information about their frequencies and possible risk factors.

Griel, W. et al., 2013: Their study was investigated the frequency of severe ADR from psychiatric patients in relation to their age. They found 699 patients exhibited severe ADRs as 517 patients upto 60 years and 182 patients were 60 years.

Kukreja, S. et al., 2013: They reviewed the polypharmacy in psychiatry. Accordingly, psychiatry polypharmacy refers to the prescription of two or more psychiatric medications concurrently to a patient. It can be categorized as same-class, multi-class, adjunctive, augmentation and total polypharmacy. Despite advances in psychopharmacology and a better understanding of the principles of therapeutics, its practice is increasing rapidly. The prevalence of polypharmacy in psychiatry varies between 13% - 90%. There are various clinical and pharmacoeconomic factors associated factors. Education, guidelines and algorithms for the appropriate management of various conditions are effective ways to avoid irrational polypharmacy.

Lahon, K. et al., 2012: They monitored the ADR of antipsychotics, antidepressants, mood stabilizers in a psychiatric department. It was a retrospective study in outpatient department in which total 115 ADRs were reported in case record in 64 patients. Olanzepine, Duloxetine, Mirtazpine were the drugs which associated maximum ADRs.

Lertxundi, U. et al., 2012: They studied about antipsychotic drugs which is related to epileptic seizures examine from spontaneous report to several Spanish and International Pharmacovigilance Databases. They found that SGA and FGA reported 169 and 35 number of convulsions respectively. They also mentioned the Reporting Odd Ratio (ROR) SGA vs. FGA i.e., 3.2.

Amor, L.B. et al., 2012: They assessed thata the safety and tolerability of first-generation and second and third generation antipsychotics in children and adolescents with schizophrenia or bipolar disorder were performed. During the study it was found that at standard doses, olanzepine and resperidone cause significant weight gain and related metabolic complications in patients treated with the medications. Quetiapine and ziprasidone displays a better tolerability profile than Resperidone and olanzepine in terms of weight gain, glucose metabolism, increase in prolactin levels, and EPS, while Aripiprazole seems to be the most weight-neutral. Most of the studies reviewed had a small sample size, a relatively short duration and a mixed diagnosis population. Systematic analyses of antipsychotics safety in young population are lacking. The selection of antipsychotics for children and adolescents should include an evaluation of their individual therapeutic benefits, safety profiles, and approval status for use in pediatric population. Further research of large samples and long-term follow-ups of these patient groups are warranted to help predict/manage the occurrence of adverse effects.

Zhang, J.P. et al., 2011: Their study includes the information about genetic variants and discussed in association with clinical drug response and side effects by the use of terms pharmacogenetics. Mechanism of action & metabolism of antipsychotic drugs studied in briefly. Genetic variants affecting drug response was explained by the detailed study on receptors and metabolic pathway of drug.

Piparva, K.G. et al., 2011: A study monitoring the adverse drug reactions due to antipsychotic drugs in a psychiatry OPD. It was a prospective study of analysis of ADR in a outpatient department of psychiatric. Conventional antipsychotics or combination of antipsychotics prescriptions were excluded in this study. Total 93 ADRs were reported from 84 prescriptions. Majority of ADRs cause by the Risperidone & Olanzepine (i.e., 82 out of 93), as they were the most commonly prescribed drugs. 78% of total events were recorded as weight gain, dizziness, sleep disturbances & appetite disturbances. Sleep & Appetite disturbance were observed in initial days of course of treatment, while EPS, fatigue, seizure, increased frequency of micturition, dizziness were observed after long term use. Role of active surveillance in post-marketing phase is also emphasized.

Shekhar, S. et al., 2011: A retrospective study of analysis of incidences, types, natures of drug related admissions was carried out in a tertiary care hospital at an interval of 12 months. Total 575 prescriptions were analyzed. They resulted that 5-10% of all hospital admissions were drug related. Drugs induced 35.5% patients by CNS, 19.8% by CVS, 12.3% by NSAIDs, 11.3% by antibiotics & 9.9% by anticoagulant. 11.3% cases were reported which induced by the hormones, cytotoxic drugs, hypolipidemia etc. The total incidence of hospital admissions due to DRP were reported as 0.20%.

Jain, T. et al., 2011: They studied the drug interactions and adverse drug reactions in hospitalized psychiatry patients. They carried out a prospective study for a duration of 6 months and number of patient were 250 aged between 18- 70 years and were prescribed with antipsychotic drugs and evaluated these patients for drug interactions and adverses drug reactions. Extrapyrimidal symptoms were evaluated at baseline and endpoint; weight gain and lipid profile were evaluated at variable time points. During the study, 463 interactions occurred; 70 were major severity, Antipsychotics were involved in 42 % of the total interactions, amongst which haloperidol (21.5%) and olanzepine (10.3%) were involved in most, while Aripiprazole (3.48%) was involved in least interactions. A total of 194 ADRs including 19 severe (5 arrythmia, 4 tremor and 10 EPS. Weight gain in the Aripiprazole vs.

Olanzepine group was 0.23 kg vs. 2.74 kg ($p<0.001$). Patients on olanzepine vs. Aripiprazole experienced elevated total cholesterol (6.7 mg/dl vs. -11.2 mg/dl), low density lipoprotein (4.3 mg/dl vs. -13.2 mg/dl), and triglycerides levels (12.7 mg/dl vs. -22.13 mg/dl). Reasons of noncompliance and inadequate clinical improvement in schizophrenia are long-term medication, ADRs and drug interactions. ADRs and drug interactions were least in Aripiprazole prescriptions. Further long-term studies are required.

Pope, A. et al., 2010: They identified how safety and tolerability data were collected and reported in recent clinical studies of antipsychotics. They conducted a survey of all 167 eligible studies published between 2002 and 2007 on the Cochrane most frequently assessed. A minority of reports addressed metabolic abnormalities, aversive subjective experiences and sexual dysfunction. Published rating scale was frequently used to evaluate EPS, but systemic methods were rarely applied to other treatment-emergent problems. The definition of individual adverse effects and the manner of reporting were inconsistent. The way in which safety and tolerability data were collected and reported in clinical studies does not allow for fair and meaningful comparison of the relative risk profiles of individual antipsychotic drugs.
Guillen, J.M.B. et al., 2009: They reviewed the use of antipsychoticsduring pregnancy and breastfeeding. They reviewed that there is growing acceptance that pregnancy itself is not protective factor against mental disorders. Indeed, some mental disorders such as psychotic and bipolar disorders may become worse during pregnancy and the immediate postpartum period. In pregnant women with a mental disorder that can be treated with antipsychotics, the known risks are – teratogenic, obestric, neonatal and those affecting the mother indicate that, in general the risks of antipsychotics and that the reduction is psychoticism improves the overall prognosis of these women. All the antipsychotics marketed in Spain are included in Category C of the US Foodand Drug Administration (USFDA), with the exception of Clozapine and the piperazine, which are included in category B. The use of all of these drugs should be avoided during breastfeeding as far as possible. The most reliable current recommendations indicate that optimal control of severe mental disorders should be maintained during pregnancy, the postpartum and subsequent periods. These recommendations also indicate that women with mental disorders must be considered as high risk and that both these women and their pregnancies should be constantly monitored.

Marum, R.J.V. et al., 2007: They evaluate the risk factors which contributing towards the occurrence of hypothermia (i.e., ADR of antipsychotic drug use). They were searched on the

basis of the WHO International Database. They concluded that hypothermia risk increase in the first days following start or dose increase of antipsychotic drugs. 55% of hypothermia patients were reported of atypical antipsychotic drugs.

3. AIM & OBJECTIVE

3.1 AIM: Detection & Monitoring of Adverse Drug Reaction due to Antipsychotic Drugs in a tertiary care hospital.

3.2 OBJECTIVES

i) To identify antipsychotic drugs most commonly responsible for ADRs.
ii) To identify the nature, incidences of ADR due to Antipsychotic Drugs.
iii) To evaluate the impact of various factors contributing towards the occurrence of ADR.
iv) To assess the causality of ADR as per Naranjo's Monitoring Scale.

4. METHODOLOGY

4.1 STUDY DESIGN

It was a prospective observational study conducted in a tertiary care hospital in city of Dehradun to detect & monitor of ADR due to Antipsychotic Drugs.

4.2 STUDY SITE

The patient was carried out in psychiatric department of a tertiary care hospital Shri Mehant Indresh Hospital, Patel Nagar, Dehradun.

4.3 STUDY POPULATION

4.3.1 Inclusion Criteria

- The patients admitted in the psychiatric department of SMIH.
- Patients of any age group of either gender who develop ADRs due to Antipsychotic drugs.

4.3.2 Exclusion Criteria

- Patients admitted in ICU.
- Patients not willing to participate in the study.
- ADR due to Drug abuse, overdose.

4.4 SOURCES OF DATA

- Inpatient profile form.

- Patient history records.
- Laboratory data record.
- ADR Reporting form.

4.5 DURATION OF STUDY

The duration of conducting the study was of six months from the psychiatric department of Shri Mehant Indresh Hospital, Dehradun.

4.6 Ethics Committee

The Ethics Committee approval was also obtained for the study and informed consent was obtained from each participant women.

4.7 STUDY DOCUMENT

Patient profile document was designed for data collection of patients including medical, medication history, present illness, current medication, laboratory data & day to day assessment.

4.8 STUDY PROCEDURE

All patients were reviewed on the daily basis. The inpatient profile form, patient history records, laboratory data was evaluated. If any suspected ADR is detected, all the details related to the suspected drug viz type of drug, dose of drug, date of starting the drug, duration of drug, & adverse drug reaction viz types of reaction, severity of reactions was noted in the ADR Reporting Form. Under suspected Medicine, name of drug, brand of manufacturer, generic names of manufacturer as well as reason of prescribing suspected drug were also assessed.

The information of de-challenge & re-challenge, concomitant medical treatment record, the relevant laboratory biochemical abnormality was also recorded.

All the detail collected in a suitable design document for suspected drug reaction filled in ADR Form. The causality assessment of the reported ADRs was carried out using the "Naranjo Causality Scale".

5. RESULT

A total number of patients included in the study were 100 of both the sex. During the study period of six months, a total of 144 ADRs were detected and recorded. Patients who were

admitted in the psychiatric department of the hospital were reviewed and monitored actively for the occurrences of ADRs.

Details of ADRs reported in the psychiatric department

During the study period of majority of ADRs detected in males in comparison to the females and the age duration mostly affected between 20 to 39 years of age.

Table 5.1: Age wise distribution of ADRs in psychiatric department.

Age	Male (%)	Female (%)	Total (%)
11-19	3(8.10%)	2(2.50%)	5(13.51%)
20-39	15(40.54%)	5(13.51%)	20(54.05%)
40-59	8(21.62%)	2(5.40%)	10(27.02%)
≥60	1(2.70%)	1(2.70%)	2(5.40%)
Total	27(72.97%)	10(27.02%)	37(100%)

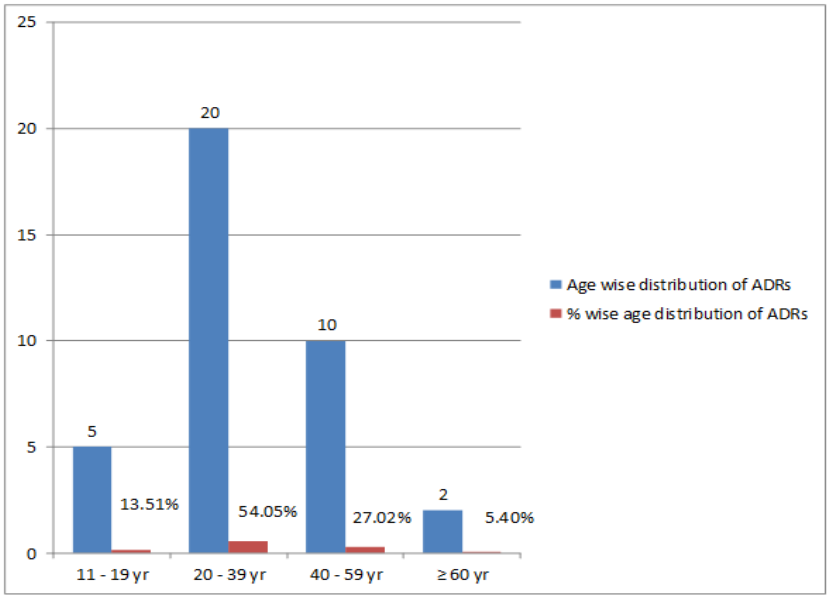

Fig. 5.1. Shows Age wise distribution of ADRs due to Antipsychotic drugs.

The most commonly prescribed antipsychotic drugs which was found to be associated with majority of ADRs was Olanzepine (41.67%) followed by Haloperidol (18.06%), Resperidone (11.11%), Quetiapine (11.11%), Amisulpride (9.03%), Aripiprazole (4.86%), Trifluoperazine (4.17%).

Table 5.2: Therapeutic class of antipsychotics implicated to cause ADR in Psychiatric department.

Name of Drug	Class of Drug	No. of ADRs	% of ADR in various classes
Olanzepine	Atypical antipsychotic	60	41.66%

Haloperidol	Typical antipsychotic	26	18.05%
Resperidone	Atypical antipsychotic	16	11.11%
Quetiapine	Atypical antipsychotic	16	11.11%
Amisulpride	Atypical antipsychotic	13	9.02%
Aripiprazole	Atypical antipsychotic	7	4.86%
Trifluoperazine	Typical antipsychotic	6	4.16%

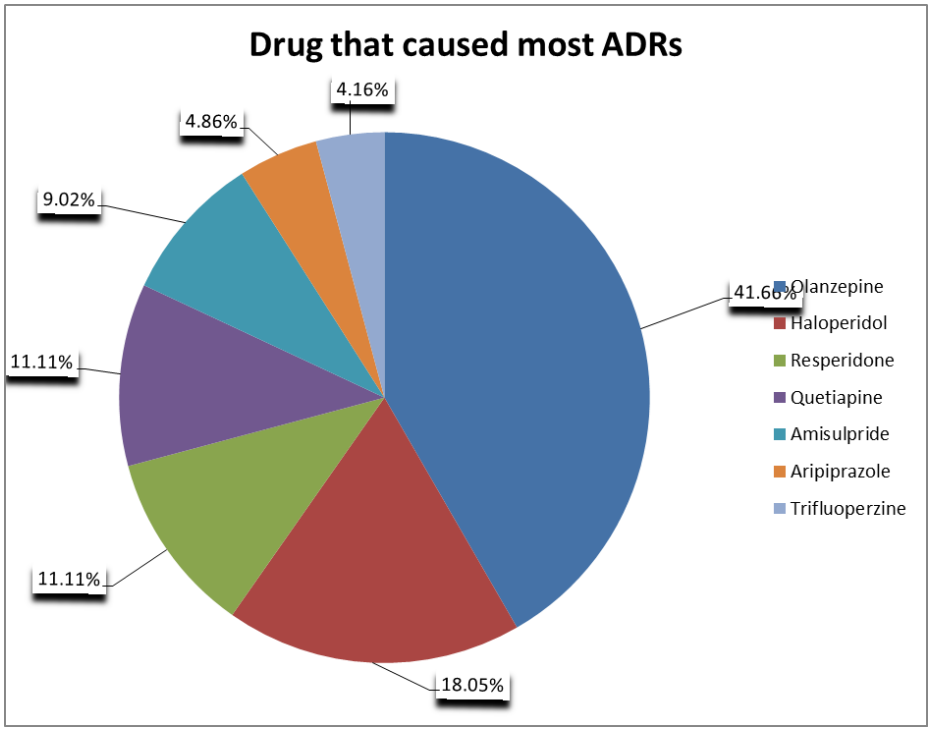

Fig. 5.2: Shows Antipsychotic drugs causing ADRs.

The most commonly reported ADR observed in our study was restlessness (15.97%), followed by insomnia (11.11%), abdominal discomfort (9.03%), Sedation (7.64%), Palcipitation (6.94%), Ghabrahat (6.25%), Tremor, bodyache, Akathesia in (5.56%) cases each, Fever (4.86%), , Dryness of mouth (4.16%), decreased Appetite, Parkinsonism (3.47%) each case, Urinary retention problem, Mild Intellectual disability in (2.78%) cases each, Tardive Dyskinesia, Dystonia in (1.39%) cases each, Diminished of Vision, headache, Inc. triglyceride level in (0.69%) cases each.

Table 5.3: Adverse drug reactions reported by Antipsychotic drugs in psychiatric department.

Type of Reactions	No. of ADRs	%
Restlessness	23	15.97%
Insomnia	16	11.11%
Abdominal Discomfort	13	9.02%
Sedation	11	7.63%

Palcipitation	10	6.94%
Ghabrahat	9	6.25%
Tremor	8	5.55%
Bodyache	8	5.55%
Akathesia	8	5.55%
Fever	7	4.86%
Dryness of mouth	6	4.16%
Parkinsonism	5	3.47%
Decreased Appetite	5	3.47%
Mild Intellectual Disability	4	2.77%
Urinary Retention Problem	4	2.77%
Tardive Dyskinesia	2	1.38%
Dystonia	2	1.38%
Diminished of vision	1	0.69%
Headache	1	0.69%
Inc, triglyceride level	1	0.69%

Fig.5.3. Shows ADR caused by Antipsychotic drugs.

According to WHO-ADR classification, the most occurred 108(79.41%) case were of type A followed by 28(20.59%) case were of type B.

Table 5.4: Classification of ADR according to WHO in psychiatric department.

Type of ADR	No. of ADRs Reported	%
Type A (Augmented)	109	75.69%
Type B (Bizarre)	35	24.30%
Type C (Continue use)	0	0
Type D (Delayed use)	0	0

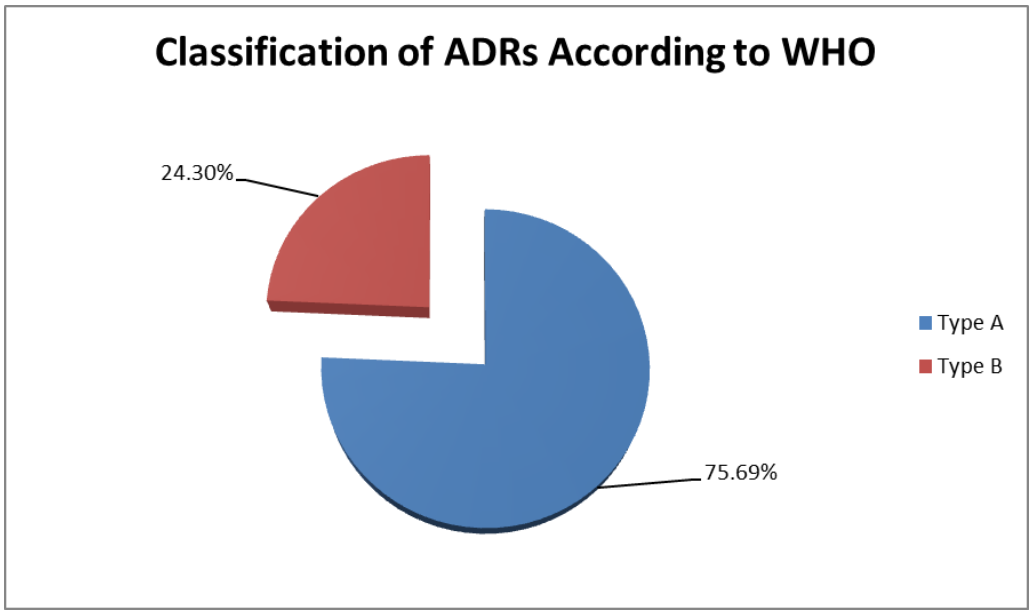

Fig.5.4. Shows percentage of ADRs type Caused due to Antipsychotic drugs.

During the study out of 37 subjects 21(56.76%) cases recovered that suffered from ADRs, while 16(43.24%) cases were reported to be recovering and there was no fatal outcome observed.

Table 5.5: Outcome of ADR reported due to Antipsychotic Drugs.

Parameters	No. of ADRs	Percentage%
Fatal	0	0
Recovering	12	27.27%
Recovered	32	72.72%
Unknown	0	0
Others	0	0

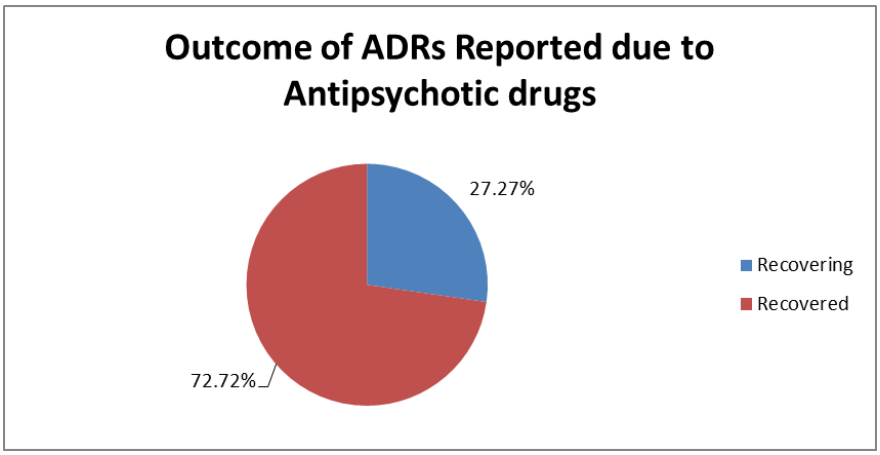

Fig. 5.5: Shows outcome of ADRs reported due to Antipsychotic drugs.

The seriousness of reaction that required intervention to prevent permanent impairment/ damage was 34(91.89%) and number of cases needs prolonged hospitalization was 3(8.11%).

Table 5.6: Seriousness of reaction observed due to Antipsychotic drugs.

Parameters	No. of ADRs	Percentage (%)
Death	0	0
Life Threatening	0	0
Congenital-anomaly	0	0
Required intervention to prevent permanent impairment/damage	39	88.63%
Prolonged Hospitalization	5	11.36%
Disability	0	0
Others	0	0

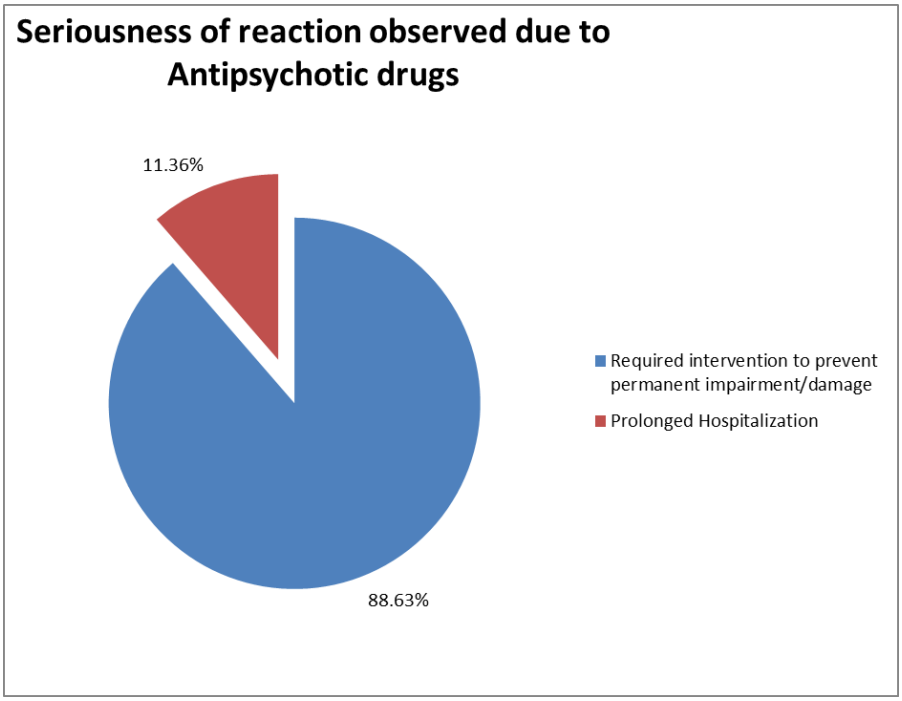

Fig. 5.6: Shows Seriousness of reactions observed due to Antipsychotic Drugs.

According to Naranjo scale, the causality assessment of suspected ADRs, it was found that 1(2.44%) case was definite, 27(65.85%) cases were probable and 13(31.71%) cases were possible.

Table 5.7: Causality assessment according to Naranjo Scale of ADRs due to Antipsychotic drugs.

Causality assessment	No. of ADRs	Percentage (%)
Definite	1	2.27%
Probable	39	88.63%
Possible	4	9.09%
Unlikely	0	0

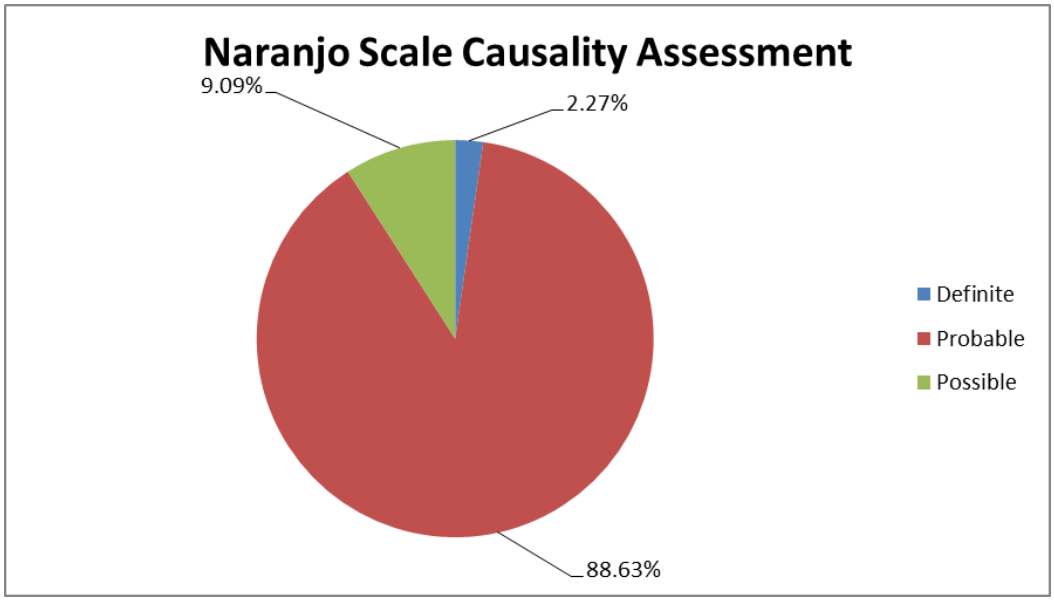

Fig. 5.7: Shows Causality of ADRs due to Antipsychotic Drugs.

6. DISCUSSION

In the pharmacotherapy of various diseases, most of the drugs are likely to have a dual-effect-beneficial as well as adverse. So, the best way to control these adverse effects is to have a triple pronged approach of prevention, treatment and rehabilition.

Pharmacovigilance is the program conducted worldwide to report various adverse reactions occurring due to drugs that are already being marketed. There is paucity of such data in India & only few studies have so far been conducted in this context. The antipsychotics drugs present a variety of different types of ADRs and lead to noncompliance or even discontinuation of therapy. Atypical Antipsychotics are now considered as first line agents based on treatment efficacy, better tolerability, & reduce risk of extra-pyramidal symptoms. A Knowledge, Practice & Attitude based study conducted in Norway found that ADRs can be prevented by collecting reliable information about their frequencies & possible risk factors.

This prospective study highlights the incidence and pattern of ADRs due to Antipsychotics in a tertiary care hospital of the country. During the six month duration of study, total 144 suspected ADRs due to antipsychotic drugs were monitored and detected among admitted patients in the psychiatry ward of the hospital.

In our study, we found that majority of subjects affected by ADRs were from adult Population (19-39 years of age). The results were similar to those reported by the other similar kind of studies (Sengupta, G. et al., 2011; Piparva, K.G. et al., 2011; Ho, Y.F. et al.,

2002; Lahon, K. et al., 2012). Most of the studies found that the most affected population due to ADR is adult population and previous studies have quoted mean age of patients with ADRs within the range observed in our study. (Sengupta, G. et al., 2011; Sarumathy, S. et al., 2014) The reason for the increased incidence of ADR in adult population was most likely due to decreased BMR, concomitant diseases and organ dysfunction (Gallelli, L. et al., 2002). Also increased sensitivity to drug effects among the elderly patients results from changes in pharmacokinetics & pharmacodynamics. Age related losses of physiologic function may also predispose the older patients to adverse drug reactions.

We found in our study that both the genders (male 27(72.97%)) and females (10(27.02%)) were at greater risk of ADR occurrence. Among the patients who developed ADRs, the percentage of male patients was predominance over female patients. Our results is somewhat supported by a recent study which shows that higher incidence of ADRs has been reported for males 54.87% and 45.12% in females and in contrast to another study 68.05% of ADR were reported in men Population (Pope, A. et al., 2010; Kurmi, P. et al., 2015). Individuals differ in their response to drug metabolisms due to various factors that include differences in body mass index, genetic constitution, difference on the level of various enzymes responsible for drug metabolisms.

The most common antipsychotic drug responsible for ADR in this study was Olanzepine (41.66%) followed by Haloperidol (18.05%), Quetiapine (11.11%), Resperidone (11.11%), and the most common ADR was restlessness among (15.97%) patients, followed by insomnia among (11.11%) subjects, Abdominal discomfort among (9.02%) patients, Sedation among (7.63%) patients, Palcipitation among (6.94%) patients, Ghabrahat in (6.25%) patients, tremor, Body ache and Akathesia among (5.55%) subjects each, fever in (4.86%) patients, dryness of mouth in (4.16%) patients, Parkinsonism and Dec. Appetite among (3.47%) subjects each, Mild Intellectual Disability & Urinary retention problem among (2.77%) patients each, Tardive Dyskinesia & Dystonia among (1.38%) patients each, Diminished of vision, Headache, Inc. triglyceride & cholesterol among (0.69%) patients each. Earlier studies are also suggestive that Resperidone, Chlorpromazine and Olanzepine were the drugs causing maximum ADRs and extra pyramidal symptoms, annticholinergic side effects and weight gain were common ADRs (Munoli. S. et al., 2016).

In this study ADR according to WHO-ADR classification analysis, we found most episodes were type A. Cause of maximum Type A reaction was difficult to explain in our study.

Outcome of the reaction showed that (72.72%) were fully recovered followed by (27.27%) recovering patients. As per earlier studies type A adverse drug reaction was common among the subjects who developed ADRs and we suggests that better management is required for the drug therapy(Hemlata, V.E. et al., 2014; Ho, Y.F. et al., 2002; Lahon, K. et al., 2012).

The seriousness of reaction that required intervention to prevent permanent impairment /damage was (88.63%) & (11.36%) cases needs prolonged hospitalization.

In this study, according to Naranjo scale the causality assessments was mostly probable in(88.63%)cases, followed by definite in (2.27%) cases & possible (9.09%) in cases. As per the recent studies most of the adverse drug reactions among cases were assessed as possible and somewhat were assessed as probable (Guillen, J.M.B. et al.,2009; Hemlata, V.E. et al.,2014; Lakshmi. P. et al.,2014; Ho, Y.F. et al., 2002; Lahon, K. et al., 2012). These observations therefore pose a threat on the use of antipsychotic medications & thus clinicians must remain aware of the ill consequences of incorporating antipsychotics in the therapeutic regimen of the patients.

The present study hints that pharmacist involvement may not only greatly increase the reporting rate but also quality of reporting. It is suggested that the most appropriate approach of medication control to minimize the incidence of ADR is screening the total medication of the individual patient by taking history of allergy as well as past medication & medical history. Hospital / Clinical Pharmacists have also a great role to play in the area of Pharmacovigilance to strengthen the National Pharmacovigilance Program.

There are certain points to be noted when prescribing drugs in psychiatry which will help reduce ADRs. Single drug should be used in lowest possible dose as far as possible. Use of more than one drug is advised only when single drug is demonstrably inadequate. When a drug is administered, target symptoms should be clearly documented. Antipsychotics should not be used as sedatives. Response to drugs should be assessed using recognized rating scale to reduce drug dosage. Close monitoring of physical health such as monitoring blood pressure, baseline blood investigations, & electrocardiogram should be done. Selection of drug should be patient specific, example in patients with cardiac disease avoid cardio toxic drugs. This helps prevent the incidence of ADR.

Non pharmacological management such as electroconvulsive therapy (ECT), behavioral therapy, & supportive psychotherapy to patients & bystanders can be combined with drug therapy. ECT & repeated transcranial magnetic stimulation is also useful in managing extra pyramidal side effects. Specific investigations to look for metabolic & other ADRs should be done according to drug prescribed.

7. CONCLUSION

Thus, it can be concluded that ADR is a significant limitation to the success of therapeutics. In order to deal with this problem Pharmacovigilance was initiated. It is essential to improve programs in health care facilities. The present study add to the existing information on the frequency & pattern of ADRs following antipsychotics medication from the other centers where such studies already been conducted & also create awareness among our own health care professionals about the importance of carrying out active surveillance studies regarding association of ADRs with antipsychotics drugs which would be the first step in trying to prevent them.

Present study depicted an overview of the different type of ADRs encountered in a tertiary care hospital. It highlighted that ADR is mostly prevalent among the elder individuals which was most frequently due to decreased BMR, concomitant disease condition etc. Among patients reported ADR, male have been reported to be at greater risk of ADR than female. The actual reason of developing ADR more than in male was differ in their response to drug metabolisms due to various factors that include differences in body mass index, genetic constitution, difference on the level of various enzymes responsible for drug metabolisms.

The most common antipsychotic drugs responsible for developing ADR in this study was Olanzepine, Haloperidol, Quetiapine, Resperidone, Amisulpride, Aripiprazole, Trifluoperazine and the most common ADRs were restlessness, insomnia, Abdominal discomfort, sedation, fever, parkinsonism, tardive dyskinesia, tremor, ghabrahat, headache, urinary retention problem, akathesia, dryness of mouth, palcipitation, mild intellectual disability, Dystonia, decreased Appetite, Body ache, Diminished of vision, Inc. triglyceride & cholesterol. Our findings suggest that second generation Antipsychotic may cause a greater risk than first generation antipsychotics, but not only due to Olanzepine. Haloperidol, Quetiapine, Resperidone, may also carry a higher risk. Thus, a cautious approach seems advisable when prescribing these drugs to patients with known risk factors.

According to WHO-ADR classification analysis, we found that most episodes were of Type-A. Among these affected patients maximum numbers of patients have been fully recovered while others were still recovering patients, hence it suggests that better management is required for drug therapy. Occurrence of ADR had largely affected hospital stay of patients indirectly influencing economic burden on the patients. Mild reactions did not require any change in prescribed drug and increase in the hospital stay, but moderate reactions require immediate stop of causative drug therapy and substitution with alternative drug and also treatment to the reaction. Causality assessment of the reported ADRs was done according to "Naranjo Scale". The reactions were mostly probable, followed by definite, and possible. The results were comparable with similar assessment in previous studies.

This study is helpful in selection of appropriate medicines for antipsychotics patients, enhancing patient adherence with the therapy by selecting medicines of lesser ADR profile, reducing unnecessary economic burden to the patients due to unwanted effects of therapy. There is a great need to create awareness and to promote the reporting of ADR which will lay a solid foundation for these health care professionals to be diligently involved in quality Pharmacovigilance in their future practices. Pharmacists & health care providers should join hands together to improve the scenario. A thorough knowledge of ADRs & a well established ADRs reporting system will help to reduce the occurrence of ADRs related admissions.

We recommend that several such studies of similar kind should be conducted among other institutions so as to develop strategies to improve & strengthen the Pharmacovigilance in India. These systems can only be successful, when utilized effectively & if awareness of their importance is continuously highlighted. Therefore, the setting up of an ADR monitoring centre at a more regional or hospital level & integrating it with a sound network can reveal unusual or rare ADRs which are prevalent in Indian Population. This will pave way to improve the quality of patient care by ensuring safer use of drugs.

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