"Prospective study in diabetic patients to monitor adverse drug reactions in various class of anti-diabetic drugs"

DISSERTATION

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In Partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

In Pharmacology

By

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Reg. No.

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PADMAVATHI COLLEGE OF PHARMACY

(Approved by the AICTE, NewDelhi and PCI, Affiliated to TN Dr.M.G.R Medical University,Chennai)

Krishnagiri Main Road, Periyanahalli – 635205,

Dharmapuri –Dist.

CERTIFICATE

This is to certify that the dissertation work entitled **"Prospective study in diabetic patients to monitor adverse drug reactions in various class of anti-diabetic drugs"** submitted to The TN Dr. M.G. R Medical University, Chennai, by Mrs. S. Myvizhi Selvi is partial fulfillment of the requirement of award of DEGREE OF MASTER OF PHARMACOLOGY, is based on result studies carried out by him in the Department of Pharmacology, under my direct guidance and supervision during the academic year 2013 -2014.

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This is to certify that the dissertation entitled **"Prospective study in diabetic patients to monitor adverse drug reactions in various class of anti-diabetic drugs"** Constitutes the original work carried out by Mrs. S. Myvizhi Selvi Under the guidance and supervision of Mr.V.Palanivel M.Pharm., (Ph.D) in the Department of Pharmacology, Padmavathi College of Pharmacy and Research Institute, Periyanahalli, Dharmapuri-635 205.

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DECLARATION

Here by I declare that this thesis **work "Prospective study in diabetic patients to monitor adverse drug reactions in various class of anti-diabetic drugs"** has been originally carried out by me under the guidance and supervision of Mr. V.Palanivel M.Pharm., (Ph.D) Asst.professor, Department of Pharmacology , Padmavathi College of Pharmacy and Research Institute,Dharmapuri-635205.

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CONTENTS

ABSTRACT

Aim of the study was to record and assess the adverse drug reactions during the treatment of diabetes mellitus in hospital. All the age groups and body weight groups were included in this study. Both male and female were included in this study. In-patients and out-patients receiving various anti-diabetic drugs were interviewed and reported adverse drug reactions were recorded.

Particularly patients taking treatment with metformin, gliclazide, insulin, pioglitazone and sitagliptin treated patients were assessed for adverse drug reactions. Data collected during the study period was documented and analysed using various statistical analysis after segregating age wise, body weight wise, and male and female gender wise. Finally data was analysed using Naranjo's documentation system along with WHO documentation system.

The results of the present study indicated that metformin shows diarrhea as major adverse reaction compared to other adverse reactions. This was followed by nausea/vomiting and flatulence. Other adverse reactions were abdominal discomfort, lactic acidosis, renal impairment and impaired hepatic functions. Gliclazide reported with parcreatitis as major adverse reaction followed by body weight gain, impaired hepatic functions and other minor adverse reactions. The first line therapy for type-1 diabetes, insulin has reported many adverse reactions compared to other drugs. Insulin reported hypoglycaemia as major adverse effect followed by weight gain and peripherial oedema as second largest adverse reactions. Other minor adverse reactions like hypotension, fatigure, asthenia and dyspnoea were also reported and recorded. Pioglitazone reported with weight gain and impaired hepatic functions as major adverse effect and pancreatitis, myocardial infraction were also reported. The other class of treatment DPP-4 inhibition sitagliptin was reported with impaired hepatic function

and pancreatitis which contributes to 25% each and other minor adverse effects like hypoglycaemia, renal impairment were reported.

These data were analysed using Naranjo's casualty assessment along with WHO adverse drug reaction assessment scale. WHO casualty assessment form was in agreement with Naranjo's assessment. Considering the all kind of adverse drug reactions and nature of severity there is an urgent need for setting up pharmacovigilance centres and recording the adverse reactions for cost effective and healthy India.

ABBREVIATION

ABPI	Association of the British Pharmaceutical Industry
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
ADE	Adverse Drug Event
ADRAC	Adverse Drug Reaction Advisory Committee
ADRs	Adverse Drug Reactions
ADRU	Adverse Drug Reactions Unit
AE	Adverse Events
BNF	British National Formulary
CDCSO	Central Drugs Standard Control Organization
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CSM	Committee on Safety of Medicines
CV	Cardiovascular
DM	Diabetes mellitus
DPP4	Dipeptidyl peptidase-4
e.g	Example
FDA	Food and Drug Administration
G6PD	Glucose 6-Phosphate Dehydrogenase
GIP	Glucose dependent Insulinotropic polypeptide

GLP-1	Glucogan like peptide -1
HDL	High Density Lipoprotein
Ig E	Immunoglobulin E
IP	In-Patients
MHRA	Medicines and Health-Care Products Regulatory Agency
MI	Myocardial Infarction
MIMS	Monthly Index of Medical Specialities
NAT2	N-Acetyl Transference
NGOs	Non-Governmental Organizations
NIDDM	Non-insulin dependent diabetes mellitus
NPAC	National Pharmacovigilance Advisory Committee
NSAIDs	Non-steroidal anti-inflammatory Drugs
OP	Out-Patients
PPC	Pheripheral Pharmacovigilance Centers
PV	Pharmacovigilance
PVD	Peripheral Cardiovascular Disease
TGA	Therapeutic Goods Administration
UKPDS	U.K. Prospective Diabetes Study
UMC	Upsala Monitoring Center
WHO	World Health Organization

1. INTRODUCTION

Adverse Drug Reaction

An **adverse drug reaction** (**ADR**) or **adverse drug event** (**ADE**) is an expression that describes the unwanted, negative consequences associated with the use of given medications. An ADR is a particular type of adverse effect and the meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial (Nebeker *et al*., 2004). The study of ADRs is the concern of the field known as *pharmacovigilance*.

The World Health Organization **(WHO)** defines an adverse drug reaction **(ADR)** as "Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (Dogra *et al*., 2013). The food and Drug Administration **(FDA)** defines an ADR as "an undesirable effect, reasonably associated with the use of the drug that may occur as a part or may be unpredictable in its occurrence." There are various mechanisms are involved in the cause of adverse drug reactions including allergy, nausea/vomiting etc.

The ADR reporting system

The World Health Organization Collaborating Centre for International Drug Monitoring was established in 1971 and since that the Centre collates spontaneous ADR reports from participating national centers with aims to increase the early recognition of new and unexpected ADRs. By combining reports from many countries from all over the world, very rare adverse reactions can be detected (Dogra *et al*., 2013, Vikas Dhikav *et al*., 2004).

There are different colour cards are used for ADR reporting. Australia follows blue card system and UK follows yellow card system. These reported ADRs will be analysed using Naranjo's casualty assessment to decide up on the severity.

Diabetes mellitus is the commonest endocrine disorder that affects more than 100 million people worldwide (6% of the population) and in the next 10 years it may affect about five times more people that it does now (WHO/Acadia, 1992; ADA, 1997). In India, the prevalence rate of diabetes is estimated to be 1-5% (Patel et al., 1986; Rao et al., 1989). Complications are the cause of mortality and morbidity in diabetes mellitus (DM). DM alone ranks the top ten causes of death in Western nations, and despite important improvements in its clinical management to date it has not been possible to control significantly its lethal consequences.

Diabetes mellitus

Diabetes is a metabolic disorder that is characterized by high blood glucose and either insufficient or ineffective insulin. This can be divided into three major subclasses i) type 1 diabetes mellitus, ii) type 2 diabetes mellitus and iii) Gestational diabetes, normally occurs during pregnancy may also lead to diabetes after delivery in some cases.

Type 1 diabetes mellitus:

Type 1 diabetes (previously known as insulin dependent diabetes mellitus; IDDM) is characterized by beta cell destruction by an autoimmune process usually leading to absolute insulin deficiency and acute onset, usually before 25 years of age (Jennifer Mayfield, 1998). Symptoms of type 1 diabetes usually develop over a short period, although beta cell destruction can begin years earlier. Symptoms may include increased thirst and urination, constant hunger, weight loss, blurred vision and extreme fatigue.

Type 2 diabetes mellitus:

Type 2 diabetes mellitus (previously known as non-insulin dependent diabetes mellitus; NIDDM) is characterized by insulin resistance in peripheral tissue and insulin secretory defect of the beta cell (Jennifer Mayfield, 1998). This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. Defective beta cells become exhausted, further fueling the cycle of glucose intolerance and hyperglycemia. The plasma insulin level in type 2 diabetes patients are higher than or equal to that of non diabetic control subjects (Yalow and Berson, 1960). This suggests that type 2 DM results from insulin resistance rather than insulin deficiency. However, it has become clear that both insulin resistance (Kahn, 1994) and insulin deficiency come in to play to cause hyperglycemia in type 2 DM patients. Insulin resistance and hyperinsulinemia may also be associated with hypertension and hypertriglyceridemia, decreased-high density lipoprotein (HDL) cholesterol and increased risk of atherosclerosis and cardiovascular disease (Reaven, 1988; Karam, 1992).

Gestational diabetes

Some women develop gestational diabetes late in pregnancy, though this form of diabetes usually disappears after the birth of the baby. However, women who have had gestational diabetes have a 20-50 % chance of developing type 2 diabetes within 5 to 10 years. As with type 2 diabetes, gestational diabetes occurs more often in some ethnic groups and women with family history of diabetes. Gestational diabetes is caused by hormones of pregnancy or a shortage of insulin.

Drugs treatment for diabetes mellitus:

Insulin:

Insulin is the first line therapy for type-1 diabetes mellitus. Insulin is a hormone which helps to regulate blood sugar. There are different classification of Insulin like short acting, long acting, intermediate acting and rapid acting insulin. (Goodman & Gilman's, 2006)

Biguanides / Metformin

The only available diabetes medication in the biguanides class of drugs is metformin. Biguanides prevent the liver from producing glucose and helps to improve the body's sensitivity towards insulin. Metformin is commonly used as a first line treatment for type 2 diabetes and may occasionally be prescribed, in combination with insulin, for people with type 1 diabetes. Metformin was approved in 1994 (in the USA)

Sulphonylureas

Sulphonylureas are the class of antidiabetic drug for type 2 diabetes that tends to include those drugs which end in 'ide'. The following drugs are all in the sulphonylureas class (branded names in brackets): Glibenclamide –also known as Glyburide (Daonil), Glipizide (Glucotrol), Gliquidone (Glurenorm), Glyclopyramide (Deamelin-S), Glimepiride (Amaryl) Gliclazide (Diamicron).

Meglitinides / Prandial glucose regulator / Glinides

The glinides are a class of drug which have a similar response as sulphonylureas but act for a shorter time. Meglitinides are prescribed to be taken by people with type 2 diabetes within half an hour before eating.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors, such as acarbose (marketed as Precose or Glucobay) or miglitol (branded as Glyset) are drugs for type 2 diabetes which slow down the digestion of carbohydrates in the small intestine and therefore can help to reduce after meal blood sugar levels. (Goodman & Gilman's, 2006)

Thiazolidinedione / Glitazones

Thiazolidinediones, also known as glitazones, are a medication for type 2 diabetes which helps to improve insulin sensitivity and have been found to help decrease triglyceride levels. However, these have recently been in public spotlight as questions over their long term safety. In September 2010, the most popularly prescribed drug in this class rosiglitazone (Avandia) was banned for use by the European medicines Agency over heart attack concerns. Pioglitazone works by making cells more sensitive to insulin, which is used to regulate the level of glucose in the body. Improving insulin sensitivity (or reducing insulin resistance) makes it easier for sugar (glucose) in the blood to get into the cells.

DPP-4 inhibitors / Gliptins

DPP-4 inhibitors, also known as gliptins, are a class of drug which help to stimulate the production of insulin and reduce the production of glucagon, particularly during digestion. DPP-4 inhibitors are usually prescribed for people with type 2 diabetes who have not responded well to drugs such as metformin and sulphonylureas. This drug class includes following medications (trade names in brackets): Sitagliptin (Januvia), Vildagliptin (Galvus), Saxagliptin (Onglyza), Linagliptin (Tradjenta) –approved for use in the USA. When more of these hormones are released blood sugar levels are reduced. It is available as 100mg tablets in the market. (Goodman & Gilman's, 2006)

Incretin mimetics / GLP-1 analogues

Incretin mimetics, also known as GLP-1 analogues, are an injectable treatment for type 2 diabetes. Incretin mimetics look to mimic the effect of a group of hormones called incretins which increase the production of insulin and decrease the release of glucagon in a relatively similar way DPP-4 inhibitors.

Pharmacovigilance

Pharmacovigilance is an important and integral part of clinical research. Despite its 40 years history, pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines. When adverse effects and toxicity do appear especially, when previously unknown, it is essential that these are reported, analysed and their significance communicated effectively to an audience that has the knowledge to interpret the information, which carry an inevitable and some for all medicines there is a trade-off between the benefits and the potential for harm. In Indian scenario, we have national pharmacovigilance program and the reported adverse reactions to be recorded and reported to national pharmacovigilance program.

Impact of pharmacovigilance on diabetes

There are various class of anti-diabetic medicines are available in the market for the diabetes mellitus treatment. Drugs like insulin, pioglitazone, sitagliptin etc are available as anti-diabetic drugs. These drugs are belongs to certain classification. Those chemical classification would have got some adverse effects and they could have been withdrawn from the market like rosiglitazone (thiozolidinethione derivative). From the same chemical class, pioglitazone is available in the market. So certain adverse effects belongs to that chemical

class like body weight gain, fluid retention etc can be monitored. DPP-4 inhibitors are known for hepatic impairment and biguanides (metformin) are known for pancreaatitis. So these adverse effects needs to be recorded and patients to be advised for the reported adverse effect before the treatment. This will help them in facing the serious adverse reactions, some are fatal. In the current study, I have taken pharmacovigilance program for diabetes mellitus treatment considering anti-diabetics like insulin, gliclazide, pioglitazone, metformin and sitagliptin.

2. LITERATURE REVIEW

Adverse Drug Reaction

An **adverse drug reaction** (**ADR**) or **adverse drug event** (**ADE**) is an expression that describes the unwanted, negative consequences associated with the use of given medications. An ADR is a particular type of adverse effect and the meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial (Nebeker *et al*., 2004). The study of ADRs is the concern of the field known as *pharmacovigilance* (PV).

Adverse drugs reactions (ADRs), put simply, are noxious, unintended, and undesirable effects that occur as a result of drug treatment at doses normally used in man for the diagnosis, prophylaxis, and treatment. Although there are many terms indicating the harmful and undesirable effects of drug treatment, the term 'adverse drug reaction' describes them best. During the course of treatment, drugs prescribed to patients produce certain effects other than the desired or expected effects (Nebeker *et al*., 2004).

These cause concern both to the physician and the patient and they not only add to spiraling costs of medical treatments, but also cause a great deal or morbidity and mortality. These are generally referred to as 'side effects' and the people usually attribute these abnormal effects to either overdose or inappropriate medications prescribed by the doctor or the attending specialists (Nebeker *et al*., 2004). The unwanted effects are categorized into many types such as toxic effects, side effects, adverse reactions, and adverse drug events etc. depending upon the taxonomic classification used. Further, the worldwide, studies have showed that ADRs are the major cause of morbidity and mortality.

Though the Indian studies in this regard are very few, the pattern of reactions seems to be similar. Moreover, we have certain peculiarities of drug use such as: large number of patients, poor doctor-patient ratio, and self-medication, drugs of alternative systems of medicine, malnutrition, widespread anemia, presence of counterfeit drugs, and presence of the highest number of drug combinational products in the world (Vikas *et al*., 2004).

Therefore, incidence of the adverse drug reactions is likely to be same as that of the West, or more (Vikas *et al*., 2004). Unfortunately, in spite of presence of five well-organized centers for drug monitoring in the country, the number of reports sent annually is dismal. This calls for the urgent need to reinforce the monitoring of adverse reactions with the help of public education against self-medication, inclusion of reaction monitoring, and an introduction to drug-safety in the curriculum of medical undergraduates, and systemic and periodic continuing medical education of health professionals. This multi-pronged strategy can lead to reduction in the incidence of adverse drug reactions.

Definition

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (Dogra *et al*., 2013). The food and Drug Administration (FDA) defines an ADR as "an undesirable effect, reasonably associated with the use of the drug that may occur as a part or may be unpredictable in its occurrence." On the other hand, adverse drug event (ADE) may be defined as an injury resulting from medical intervention related to a drug which appears to be a more comprehensive and clinically relevant description of the problem than does ADR (Dogra *et al*., 2013).

PREDISPOSING FACTORS

There are many factors that can predispose to the occurrence of adverse drug reactions in a patient who have one or more of the following predisposing factors are at high risk of developing ADRs.

Polypharmacy:

Patients with multiple drug therapy are more prone to develop an adverse drug reaction either due to alteration of drug effect through an interaction mechanism or by synergistic effect (Fulton *et al*., 2005). The amount of risk associated with multiple drug therapy increases in direct proportion to the number of drugs administered (Dogra *et al*., 2013, Classen *et al*., 2005).

Age:

Elderly and pediatric are more vulnerable to develop ADRs. Elderly patients are more susceptible to ADRs to the physiological changes (pharmacokinetic and pharmacodynamics) which accompany aging, and also because they are often taking many drugs for chronic and multiple diseases. Pediatric patients may develop serious adverse drug reactions to some drugs since all children, especially neonates, differ in their drug handling capacity compared to adults. An example of such s serious reaction is the gray baby syndrome with chloramphenicol (Dogra *et al*., 2013).

Drugs characteristics:

Some drugs are highly toxic in nature and patient who are treated with these agents are at an increased risk of ADRs. For example, nausea and vomiting is a common adverse drug reaction seen in patients with antinuclear drugs. Also, patients who are treated with drugs, which have a narrow therapeutic index such as digoxin and gentamycin, are more

susceptible to develop ADRs, as a slight increase in the serum drug concentration of these drugs may result in drug toxicity (Dogra *et al*., 2013).

Gender:

It has been reported that women are more susceptible to develop an ADR, for unknown reasons. Cholramphenicol induced aplastic anemia and phenylbutazone induced agranulocytosis is twice and thrice as common, respectively in women patients (Dogra *et al*., 2013).

Race and genetics:

It is evident that ADRs are more common in genetically predisposed individual. For example, patients who are genetically deficient of glucose 6-phosphate dehydrogenase (G6PD) enzyme are at higher risk of developing hemolysis due to primaquine as compared to genetically eficient. Race as well as genetic polymorphism may account for alterations in handling of drugs and their end organ effects (Dogra *et al*., 2013).

CAUSES AND CLASSIFICATION OF ADVERSE DRUG REACTIONS

Basically two different mechanisms are involved and is responsible for the developing ADRs which are as follows:

The first Type A is an extension of the normal pharmacological effect of a drug or its metabolites. The second Type B is unrelated to the normal pharmacogical effect of the drug. Type A reactions are usually predictable, dose or clearance dependent, and most often preventable whereas type B reactions are idiosyncratic, often allergic or immunogenic in nature, neither dose nor clearance dependent, and rarely avoidable (Dogra *et al*., 2013).

Further type B reaction can be divided by the type of immune mediator involved, i.e., IgM, or T cell. Another type of ADR results from the long term use of a drug, with the cumulative dose, being the causative factor and such reaction would be cardio toxic which may occurs after prolonged cumulative dosing with Doxorubicin. Delayed effect of drugs or their metabolites, i.e., teratogrnicity, car cinogenicity, also may be considered to be mechanism of adverse drug reactions.

The Gell and Coombs classification system describes the predominant immune mechanisms that lead to clinical symptoms of drug hypersensitivity. This classification system includes type I reactions (IgE-mediated); n type II reactions (Cytotoxic); Type III reactions (immune complex); and Type IV reactions (delayed, cell-mediated). However, some drug hypersensitivity reactions are difficult to classify because of a lack of evidence supporting a predominant immunologic mechanism. These include certain cutaneous drug reactions (i.e., maculopapular rashes, erthroderma, exfoliative dermatitis, and fixed drug reactions) and specific drug hypersensitivity syndromes. Unpredictable nonimmune drug reactions can be classified as pseudoallergic, idiosyncratic or intolerance. Pseudoallergic reactions are the result of direct mast cell activation and degranulation by drugs such as opiates, vancomycin (Vancocin), and radio contrast media. These reactions may be clinically indistinguishable from Type I hypersensitivity, but do not involve drug-specific IgE. Idiosyncratic reactions are qualitatively aberrant that cannot be explained by know the pharmacologic action of the drug and occur only in a small percent of the population. A classic example of an idiosyncratic reaction is drug included hemolysis in persons with glucose-6- phosphate dehydrogenase (G6PD) deficiency. Drug intolerance is defined as a lower threshold to the normal pharmacologic action of a drug, such as tinnitus after a single average dose of aspirin (Dogra *et al*., 2013).

The ADRs are occasionally classified as acute, sub-acute, or latent according to their onset or severity. Acute events are those observed within 60 minutes after the administration of a medication and include anaphylactic shock, severe bronchconstruction, and nausea or vomiting. Sub-acute reactions occur within 1 to 24 hours and include maculopapular rash, serum sickness, allergic vacuities and antibiotic-associated diarrhea or colitis. Whereas. The latent reactions require 2 or more days to become apparent and include eczematous eruptions, organ toxicity, and tardive dyskinesia (Dogra *et al*., 2013).. Further, ADRs can also be classified as mild, moderate, or severe and mild reactions may include dysgyesia associated with clarithromycin, are bothersome but may not require a change in therapy, additional treatment, or continued hospitalization. Reactions that are disabling or life-threatening, or those that considerably prolong hospitalization, are classified as severe.

The classification of Rawlins and Thompson is perhaps the most widely used to describe adverse drug reactions. Adverse reactions are categorized as Type A or B. Type reactions are those that extend directly from a drug pharmacological effect. They are often predictable and dose-dependent. Type A reactions also include adverse effects resulting from drug overdose and drug-drug interactions. Sedation caused by an antihistamine or hypotension caused by a beta-adrenergic antagonist is considered Type A reactions. Type B reactions are idiosyncratic or immunologic reactions that are often rare and unpredictable. Examples of Type B reactions include aplastic anemia by chloramphenicol or rash included by betalactam antibiotics. Albeit not universally accepted, other authors have extended this classification system to include Types C, D and E reactions to describe chemical, delayed, and end-of-treatment reactions, respectively. Will and Brown have proposed, on the basis of mechanism, eight categories of ADR. (Dogra *et al*., 2013).

Type A (Augmented):

Type-A reactions are dose related actions of a medicine upon the human body, which could have been predicated based upon knowledge of this mode of action and pharmacology of a drug or excipient. These reactions are the most common type of adverse reactions and improve if medicine is withdrawn (Vikas Dhikav *et al*., 2004). Predictable by the pharmacological mechanisms, e.g., hypotension by beta-blockers, hypoglycemia caused by insulin or oral hypoglycemic, or NSAID included gastric ulcers

Type B (Bugs/ Bizarre):

These reactions rely upon promoting the growth the certain micro-organism. Type B reactions are pharmacologically predictable events and improve if medicine is withdrawn. Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, serious, can be final; unrelated to the dose, e.g., hepatitis caused by halothane, a plastic anaemias caused by chloramphenicol, neuroleptic malignant syndrome caused by some anesthetics and anti-psychotic (Vikas Dhikav *et al*., 2004).

Type C (Chemical):

A number of adverse reactions depend upon the chemical nature of a drug or excipient rather than pharmacological properties. The severity of this reaction is more a function of concentration of the offending substance than dose.

Type D (Delivery/Delayed):

A variety of adverse reactions occur as a specific consequence of the method of drug delivery. This reaction does not depend upon the chemical or pharmacological properties but occurs because of the physical nature of the formulation and/ or the method of administration. Type-d are delayed occurrence of ADRs, even after the cessation of treatment, e.g., corneal

opacities after thioridazine, ophthalmopathy after chloroquine, or pulmonary/peritoneal fibrosis by methylerzide. (Vikas Dhikav *et al*., 2004).

Type E (Exit/End of lose):

Type E reactions are known as withdrawal reactions and are a manifestation of physical dependence. It is possible for them to occur only after the administration of the medicine has ceased or the does is suddenly reduced and the reaction is linked more to duration of administration than dose. Withdrawal reactions occurs typically with the depressant drugs, e.g., hypertension and restless in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (Prazosin) or ACE inhibitors (Vikas Dhikav *et al*., 2004).

Type F (Familial/Failure of Therapy):

Certain adverse reactions occur only in susceptible individuals with genetically determined, inherited, metabolic disorders .These reactions must not be confused with those that occur because of the normal variation in ability to metabolize, a drug among population. Results from the ineffective treatment (previously excluded from analysis according to WHO definition), e.g., accelerated hypertension because of inefficient control. If adverse drug reactions are considered as any other medical illness and approached in the same way, then many questions would appear like: with timely invention, many of the adverse drug reactions can be prevented. Focus of the studies in the pharmacovigilance has now shifted from knowing the incidence, patterns, severity and predictability to prevention. Many programmes and approaches are being tired in the western countries to know what can be done to prevent the adverse drug reactions. This has made the study of pharmacovigilance more relevant than ever before (Dogra *et al*., 2013, Vikas Dhikav *et al*., 2004).

Type G (Genotoxicity):

A number of drugs can produce genetic damages in humans and notably, some are potentially carcinogenic or genotoxic. Some, but not all, teratogenic agents damage genetic material within the fetus (Vikas Dhikav *et al*., 2004).

Type H (Hypersensitivity):

Type H reactions are side effects caused by allergy or hypersensitivity. They are probably the most common adverse reactions after Type a reactions. These are many different types, but all involve activation of an immune response. They are not pharmacologically predictable and dose dependent. Occurs as a result of continuous drug use and may be irreversible, unexpected, unpredictable, e.g., tardive dyskinesias by antipsychotic, dementia by anticholinergic medications (Vikas Dhikav *et al*., 2004).

Type U (Unclassified):

Some ADRs have a mechanism that is not understood and these must remain unclassified until more is known about them. This may necessitate the introduction of new adverse reaction categories in future (Vikas Dhikav *et al*., 2004).

MECHANISM OF ADVERSE DRUG REACTION

Mechanisms of Type 'A' Adverse Drug Reactions

A drug suspected to have caused an adverse drug reaction in one patient may not necessarily cause the similar adverse reaction in another patient. This is due to inter-individual variability, which may predispose an individual to an ADR. Any type A reaction, which occurs in an individual, may be attributed to any one or more of the following mechanisms (Dogra *et al*., 2013).

Pharmaceutical causes

The possible pharmaceutical causes which might be attributed to occurrence of a type-A adverse drug reaction include changes in the drug quantity present in a particular product, and also changes in its drug release properties. For example, there are several reported reactions of gastrointestinal bleeding and hemorrhage due to a rate-controlled preparation of indomethacin. This may be due to irritant effects of high concentrations of indomethacin on a localized area of gastrointestinal mucosa. Another example is the corrosive effects on the esophagus caused by certain doxycycline salts. By changing to another salt, the risk may be reduced dramatically. To avoid such reactions, the drug regulatory authorities have laid down stringent requirements for marked drug products.

Pharmacokinetic causes

Alterations in the absorption, distribution, metabolism and elimination of drugs may alter drug effects by changing the concentration of drug present at the site of action. The change in the drug effect due to alterations in pharmacokinetic parameters may be experienced as either therapeutic failure or toxicity (Dogra *et al*., 2013).

Absorption:

Alterations in the rate and extent of drug absorption may result in adverse drug effects. The plasma concentration of a drug is partly determined by the rate at which the drug is absorbed after ingestion or injection. The plasma concentration of an orally administered drug in turn depends greatly on the gastric emptying rate. Similarly, the extent of drug absorption (the total amount of drug reaching the general circulation) also plays an important role in altered response. Following oral administration, many factors may influence the extent of drug absorption including drug formulation, gastrointestinal motility, and first pass metabolism, concomitant administration of other drugs and the absorptive capacity of

gastrointestinal mucosa. Any alteration in the rate or extent of drug absorption may result in either therapeutic failure or toxicity.

Distribution:

There are several factors, which determine the extent of distribution of a drug including regional blood flow, membrane and protein/tissue binding. Changes in drug distribution may predispose to adverse drug reactions, although the clinical significance of such mechanisms is yet to be proved.

Metabolism:

The drug handling capacity of an individual can greatly affect the drug effect. In an individual who has a reduced metabolic rate, accumulation of drug in the body may be higher, leading to increased risk of adverse drug reactions (especially type A reactions), while therapeutic failure may occur in an individual who has an enhanced metabolic rate. These changes are due to inter-individual variations in drug metabolizing capacity, which in turn is greatly influenced by genetic, environmental and other factors. For example 'slow acetylators' are highly prone to develop type A reaction to drugs which are metabolized by acetylation, such as isoniazid, dapsone, hydralazine and procainamide. Also differences in the rate of oxidation by cytochrome P450 system are of clinical importance (Dogra *et al*., 2013).

Elimination:

The major routes of excretion for many drugs are the liver and kidneys by which metabolites are being formed and excreted. One of the most important causes of type A adverse drug reaction is a change in the drug elimination rate. Drug accumulation due to reduced elimination may predispose to adverse drug reactions as a result of increased drug

concentration in plasma and tissue. Conversely, reduced concentration of drug in plasma and tissue due to enhanced drug elimination may lead to therapeutic failure.

Pharmacodynamic causes:

Increased sensitivity of target tissues or organs may predispose a person to adverse drug reactions. Although the reasons why different individuals react differently to drugs are still not clear, evidence is accumulating to suggest that target tissue or organ sensitivity is influenced by the drug receptors themselves, by homeostatic mechanisms or by disease it-self (Dogra *et al*., 2013).

Drug receptors:

Most drugs elicit their response by combining with receptors and these receptors are basically either protein molecules or enzymes. The amount and sensitivity of receptors of one individual may differ from another individual. Some individuals may have fewer specific drug receptors while others may have a higher number of less active receptors. This intervariability between different individuals can greatly affect the drug effect, when the drug acts through these specific receptors.

Homeostatic mechanisms:

Many physiological factors may determine the extent of a drug's effect in an individual as drug effects occur within the environment of the body's physiological mechanisms. For example, intravenous atropine produces a variable increase in heart rate and some individuals develop tachycardia of 160 beats per minute at a dose which is almost ineffective in others. The magnitude of the observed effect is dependant on the balance between parasympathetic and sympathetic cardiac tone, which appears to be under genetic control (Dogra *et al*., 2013).

Disease:

The pharmacological effects of a drug which are not apparent in a healthy individual may be unmasked by intercurrent diseases. An example is an asthmatic patient who develops bronchoconstriction while taking non-selective beta-blockers such as propranolol.

Mechanisms of Type 'B' Adverse Reaction

The type 'B' reactions are aberrant in terms of the normal pharmacology of the drug and they are a heterogeneous group of unpredictable adverse effects. By definition, type 'B' reactions are unrelated to the pharmacology. The major sources for type 'B' reactions include decomposition of the active ingredients, the effects of non-drug excipients (additives, preservatives, colouring and solubilising agent) and synthetic by-products of active constituents. In the majority of cases the use of decomposed drug products may result in therapeutic failure and even in some instances, though not all, the decomposed product may be highly toxic and lethal. Deaths have been reported due to decomposition of paraldehyde to acetaldehyde and its subsequent oxidation to acetic acid. There is a clear recognition of adverse drug reactions caused by excipients. Many additives including propylene glycol and carboxymethylcellulose may cause hypersensitivity reactions. The eosinophiliamyalgia syndrome associated with L-trytophan may be related to the use of preparations containing a contaminant, although a genetic factor may also be involved (Dogra *et al*., 2013).

Impact of ADRs on Health-Care Costs

In a recent estimate, the annual national cost of drug-related morbidity and mortality was placed at $ 76.6 billon, with the majority related to hospital admissions associated with drug therapy or the absence of appropriate drug therapy. Two recent studies have specifically estimated the costs of adverse drug events (James *et al*., 2004). Classen *et al* found that for patients with adverse drug events occurring during hospitalization, the hospitalization was

longer by 3.23 days and the mean cost of hospitalization was greater by $4655 than that for patients who did not experience an adverse drug event. In a more detailed analysis it was determined that the extra length of hospital stay attributable to an adverse drug event was 1.74 days and the excess cost attributable to an adverse drug event was 1.74 days and the excess cost attributable to and adverse drug event was $2013, with a range of $677 TO $9022. At their study site (LDS hospital in Salt Lake City), the authors estimated that over a 4-ys period the excess hospital cost attributable to adverse drug events were $4,482,951 and the excess hospital days were 3874. If 50% of these adverse drug events were preventable, then a successful prevention programme could save more than $500,000 annually (James *et al*., 2004).

It was observed in a case-controlled trial within a prospective co-hort study of 4108 hospital admissions, 190 adverse drug events, of which 60 were preventable and the costs attributable to an adverse drug event were $2595 for all adverse drug events and $4685 for preventable adverse drug events. The authors estimated that based on these data about the incidence of adverse drug events, the annual cost attributable to all adverse drug events, was equivalent to all health-care cost (Vikas Dhikav *et al*., 2004).

The ADR reporting system

The World Health Organization Collaborating Centre for International Drug Monitoring was established in 1971 and since that the Centre collates spontaneous ADR reports from participating national centers with aims to increase the early recognition of new and unexpected ADRs. By combining reports from many countries from all over the world, very rare adverse reactions can be detected (Dogra *et al*., 2013, Vikas Dhikav *et al*., 2004).

Blue Card System

In Australia, adverse reaction reporting is coordinated by the Adverse Drug Reactions Unit (ADRU) at the Therapeutic Goods Administration (TGA) and the system for monitoring adverse reactions is by voluntary reporting of events through health professionals and consumers. When a health professional or consumer suspects an adverse reaction to a medicine, they can report it directly to the Adverse Drug Reaction Advisory Committee (ADRAC) using a "blue card" (Michael Bollen 2003).

Healthcare professionals usually submit reports on the 'blue card' which accompanies the Australian Adverse Drug Reactions Bulletin and the Schedule of Pharmaceutical Benefits (Michael Bollen, 2003). Reports can also be made by letter, fax or electronically to http://www.tga.gov.au/problem/index.htm#medicines

UK Yellow Card System (Scott *et al*., 2005)

The yellow card scheme for reporting suspected adverse drug reactions (ADRs) was introduced in 1964 and over 400,000 reports have now been received by the Committee on Safety of Medicines (CSM)/ Medicines and Healthcare products Regulatory Agency (MHRA). They also manage a spontaneous reporting system, which asks doctors and more recently, pharmacists to report all suspected reactions to new products marked with a black triangle in the British National formulary (BNF), the Association of British Pharmaceutical Industry (ABPI) Medicines Compendium and the Monthly Index of Medical Specialties (MIMS). Doctors and pharmacists are being asked to report all serious suspected reactions to established drugs (Scott *et al*., 2005).

Standard repot forms or Yellow Cards are located inside the back cover of the BNF, MIMS, ABPI medicines compendium and on prescription pads. The consent of the patient is

not required in order to submit a Yellow Card. The minimum details required for submission are the patient initials and an identification number, the identity of the reporting doctor or pharmacist, the nature, treatment and outcome of the suspected ADR and its start and stop dates, the seriousness of the reaction, all to be completed using tick boxes (Scott *et al*., 2005).

Naranjo Causality Scale (adapted) (Naranjo *et al*., 1981)

1. Are there previous conclusive reports on this reaction?

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

2. Did the adverse event appear after the suspected drug was given?

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

3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

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

4. Did the adverse reaction appear when the drug was readministered?

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

5. Are there alternative causes that could have caused the reaction?

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

6. Did the reaction reappear when a placebo was given?

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

7. Was the drug detected in any body fluid in toxic concentrations?

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

8. 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 or not done (0)

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

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

Scoring

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

Indian Scenario

Monitoring of adverse drug reactions started in India about two decades ago (1982) under the chairmanship of the Drug Controller of India (DCI), five centers were established with the idea of starting a monitoring programme nationwide. It consisted of three phases in which the first one being monitoring of reactions in the institutes, second one in governmental bodies like Central Government Health Scheme (CGHS), and the third phase proposed to include general practitioners. A multi-institutional pilot study involving 58,194 cases was done in 1987 under the aegis of Indian Council of Medical Research (ICMR). Its nodal centre (National Pharmacovigilance Centre) is located in the Department of Pharmacology, All India Institute of Medical Sciences, and New Delhi. It is affiliated to WHO collaborating Centre for ADR Monitoring, Uppsala, Sweden. The others are located in PGI (Chandigarh), JIPMER (Pondicherry), KGMC (Lucknow), and Seth GS Medical College (Mumbai) is the special centers. It was envisaged to be a collaborative activity of both clinicians and pharmacologists. Now in India, the pharmacologists with or without the involvement of clinicians usually have to observe it (Uppal *et al*., 2008). Physicians, however, continue to play a meaningful role in the entire monitoring process, as the co-operation of the clinicians is needed to have an access to the patient data and at times in interpretation of the reports of

suspected adverse drug reactions. In many other countries, the pharmacists or nurses usually carry out it under supervision. They are specially recruited for this purpose and the physicians and pharmacologists are involved in the interpretation of the collected data or hypothesis testing on the basis of the reports. These workers may involve a panel of the physicians in reviewing all the collected reports. Though the pattern of adverse reactions differs slightly from country to country, adverse reactions to analgesics (mainly, non-steroidal anti-inflammatory drugs) and antibiotics constitute about half of all such reports in India (Uppal *et al*., 2008). This may be partly due to the fact that these are the most commonly used drugs in therapeutics. Another important drawback of clinical trials is that they can only report adverse reactions that appear within the finite duration of trial and delayed reactions would be missed.

Pharmacovigilance (PV)

Regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have many responsibilities, including the protection and promotion of public health through the evaluation and supervision of medicines for human use (EMA guidelines, 2012).

Pharmacovigilance is an important and integral part of clinical research. Despite its 40 years history, pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines. When adverse effects and toxicity do appear especially, when previously unknown, it is essential that these are reported, analysed and their significance communicated effectively to an audience that has the knowledge to interpret the information, which carry an inevitable and some for all medicines there is a trade-off between the benefits and the potential for harm. The harm can be minimized by ensuring that medicines of good

quality, safety and efficacy are used rationally and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. Taking medicines and prescribing them are among the commonest of activities of people who are unwell and of those who care for them. It makes sense that those medicines should be monitored to equally demanding standards as those evident in the development and evaluation of drugs and that prescribing habits and the extent of rational and cost-effective use should be reviewed. Responsibility for the holistic approach to drug safety that is encompassed in the science and practice of pharmacovigilance as reflected in this article has to be shared if ideal practice is to be achieved. The scientists, clinicians, pharmaceutical manufacturers, drug developers, regulators, public policy makers, patients and the general public all have their own complementary roles in achieving what is envisaged.(Dogra *et al.,* 2013). Pharmacovigilance is particularly concerned with adverse drug reactions, or ADRs, which are officially described as: "a response to a drug which is noxious and unintended, and which occurs at the doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function (Santosh and Tragulpiankit, 2011)

National Pharmacovigilance Programme (National Pharmacovigilance Protocol., 2004)

India has more than half a million qualified doctors and 15,000 hospitals having bed strength of 6, 24,000 and is the fourth largest producer of pharmaceuticals in the world. Now India is emerging as an important clinical trial hub in the world and many new drugs are being introduced by our country. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs.

Clearly aware of the enormity of task the Central Drugs Standard Control Organization (CDSCO) has initiated a well-structured and highly participative National

Pharmacovigilance Programme. It is largely based on the recommendations made in the WHO document titled Safety Monitoring of Medicinal Products-Guidelines for setting up and running a Pharmacovigilance centre. The National Pharmacovigilance Program was officially inaugurated by the Honorable Health Minister Dr. Anbumani Ramadoss on 23 November, 2004 at New Delhi.

The specific aims of the pharmacovigilance programme are to contribute the regulatory assessment for benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use. Further, to improve the patient care and safety in relation to use of medicines and to apply all medical and paramedical interventions for public health and safety. In spite of that it also promotes the better understanding, education and clinical training and its effective communication to the public.

The Programme aims to foster the culture of ADR notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO-UMC. Under this program, 26 peripheral centers, 5 regional centers and 2 zonal centers were established. The Peripheral centers are sharing the responsibility of recording the Adverse Events (AE) and also sending the information's to the regional centers. They in turn collate and scrutinize the data received from the peripheral centers and submit it to the zonal centers and the zonal centers are analyzing the data and submitting consolidated information to the National Pharmacovigilance Center. The zonal centers are also providing the training, general support and coordinating the functioning as the regional centers (National Pharmacovigilance Protocol., 2004).

The National Pharmacovigilance Advisory Committee (NPAC) oversee the performance of various zonal, regional and peripheral pharmacovigilance centers (PPC) as well as if necessary may recommend possible regulatory measures based on the data received from various centers. It also oversees data collection and assessment, interpretation of data as well as publication of ADR monitoring data. The Committee also periodically evaluates their protocol compliance levels to ensure that the data received is homogenous and can be scientifically pooled for informed regulatory decisions. Wherever necessary, NPAC also seeks the opinion of experts in various specializations.

National Pharmacovigilance Policy

Since there are social and economic consequences of adverse drug reactions and the positive benefit/cost ratio implementing appropriate risk management, there is a need to engage health-care professional and the public at large, in a well-structured programme to build synergies for monitoring adverse drug reactions. The purpose of the programme is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public.

Medium-term objectives:

To engage several healthcare professionals and NGOs in the drug monitoring and information dissemination processes.

Long-term objectives:

To achieve such operational efficiencies that would make Indian National Pharmacovigilance Programme a benchmark for global drug monitoring endeavors. Before a product is marked, experience of its safety and efficacy is limited to its use in clinical trials and the conditions under which patients are studied during the pre-marketing phase do

not necessarily reflect the way the medicine will be used in the hospital or in general practice once it is marked. Information about rare but serious adverse drug reactions, chronic toxicity, and the procedure of its use in special groups such as pregnant women, children and elderly are necessary.

Aims of Pharmacovigilance (WHO, Pharmacovigilance: ensuring the safe use of Medicines, Geneva, WHO 2004.)

- Improve patient care and safety in relation to the use of medicines, all medical and Para medical interventions.
- Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
- Pharmacovigilance keeps track of any drastic effects of drugs.
- Improve public health and safety in relation to the use of medicines.
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including costeffective) use.
- Promote understanding, education, clinical training in pharmacovigilance and its effective communication to the public

Pharmacovigilance impact on diabetes mellitus treatment

Following table and figure represents the impact of pharmacovigilence on diabetes mellitus treatment and diabetes drug development (Bailey, 2013). Considering all the above factors, it is essential to monitor the adverse drug reactions through Pharmacovigilance program for diabetes mellitus treatment.

Table 4—*Postmarketing CV outcome studies with diabetes therapies*

Trial	Test agent	Started	Years	No. pts	Primary end point
TECOS	Sitagliptin	2008	~4	~14,000	Composite of CV death, NFMI, NFS, Angh
EXAMINE	Alogliptin	2009	4.75	~5,400	Composite of CV death, NFMI, NFS
CANVAS	Canagliflozin	2009	~4	~4,400	Composite of CV death, NFMI, NFS
ACE	Acarbose	2009	~4	~7,500	Composite of CV death, NFMI, NFS
LEADER	Liraglutide	2010	~5	~9,400	Composite of CV death, NFMI, NFS
EXSCEL	Exenatide QW	2010	~5.5	9,500	Composite of CV death, NFMI, NFS
SAVOR-TIMI 53	Saxagliptin	2010	~4	16,500	Composite of CV death, NFMI, NFS
CAROLINA	Linagliptin	2010	8	6,000	Composite of CV death, NFMI, NFS, Angh
ELIXA	Lixisenatide	2010	~4	~6,000	Composite of CV death, NFMI, NFS, Angh
NCT01131676	Empagliflozin	2010	~4	~7,000	Composite of CV death, NFMI, NFS
NCT01042769	Aleglitazar	2010	~4.5	~7,000	Composite of CV death, NFMI, NFS
REWIND	Dulaglutide	2011	~6.5	~9,600	Composite of CV death, NFMI, NFS
DECLARE-TIMI 58	Dapagliflozin	2013	~6	17,150	Composite of CV death, NFMI, NFS

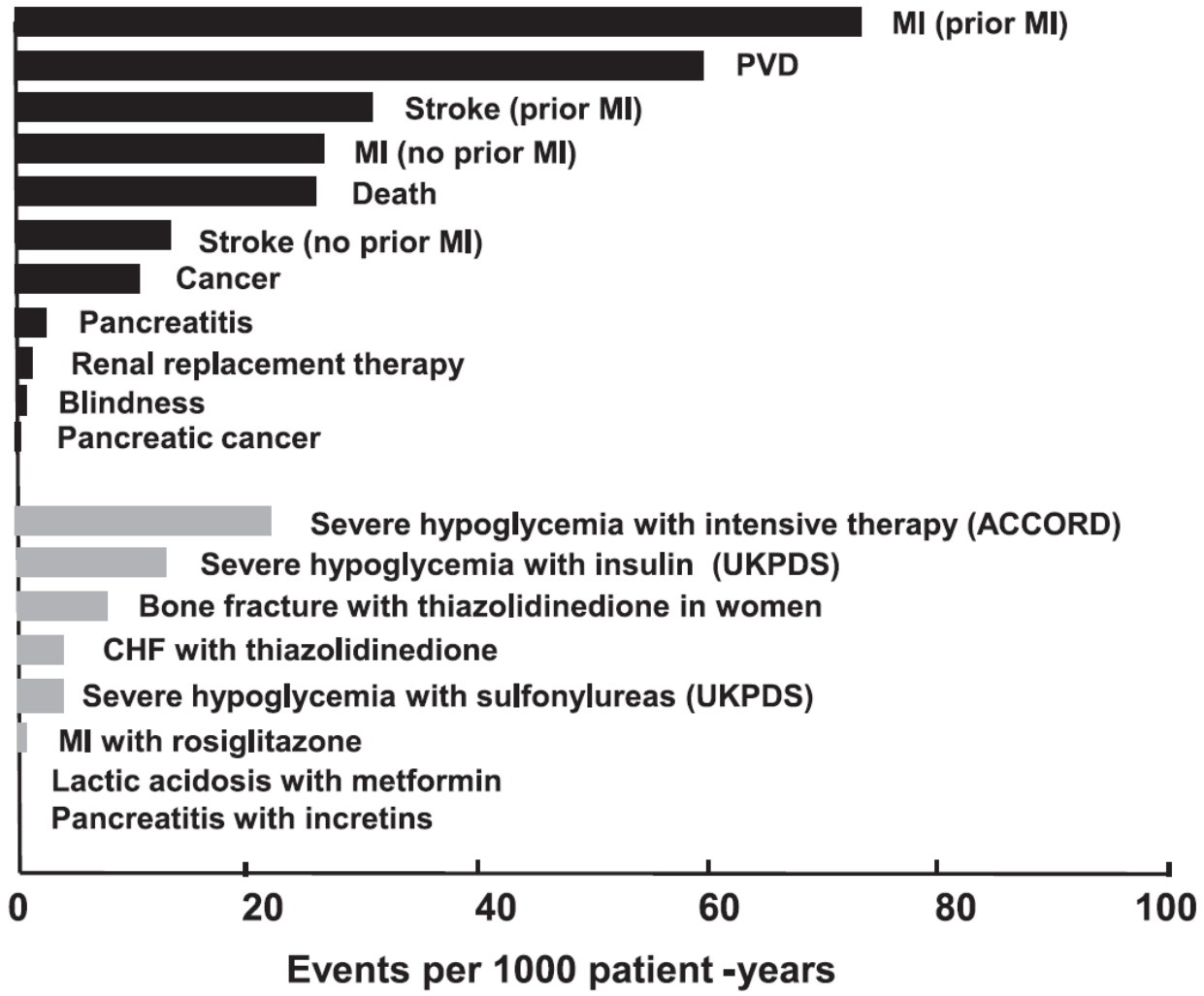


Figure 1—*Risk of diabetes complications and adverse events associated with diabetes drug therapies expressed as absolute risk per 1,000 patient-years. Black bars show representative values for risk in diabetic patients, and gray bars indicate excess risk of events in patients treated with specific glucose-lowering medications relative to diabetic patients receiving comparator therapies. Incidence rates are subject to considerable variation with age, duration of diabetes, and concomitant morbidity. Adapted with permission from Bergenstal et al. (13). Data were derived from references 13–28. ACCORD, Action to Control Cardiovascular Risk in Diabetes; CHF, congestive heart failure; PVD, peripheral vascular disease; UKPDS, U.K. Prospective Diabetes Study.*

Diabetes mellitus is the commonest endocrine disorder that affects more than 100 million people worldwide (6% of the population) and in the next 10 years it may affect about five times more people that it does now (WHO/Acadia, 1992; ADA, 1997). In India, the prevalence rate of diabetes is estimated to be 1-5% (Patel *et al*., 1986; Rao *et al*., 1989). Complications are the cause of mortality and morbidity in diabetes mellitus (DM). DM alone ranks the top ten causes of death in Western nations, and despite important improvements in its clinical management to date it has not been possible to control significantly its lethal consequences.

Diabetes mellitus

A study of ancient literature indicates that diabetes was fairly well known and well-conceived as an entity in India. The knowledge of the system of the diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age. Sushruta has accurately described diabetes around 1000 B.C. The disease was known as 'Asrava' during Vedic era (6000 B.C.) and a detailed description of it is available in Brahattrai viz.; Charaka Samhita, Susruta Samhita and Babhatta. Asthanga haridaya (600 AD) is the first medical treatise in which one gets clear definition of madhumeha/diabetes mellitus mentioning it as glycosuria (Madhviv mehati i.e. honey like urine). The word 'Prameh' (diabetes) is derived from the root 'Miha sechane' meaning of passing urine, qualify by prefix 'pra' meaning excess in both frequency and quantity [Prameha = Pra (excessive) + Meha (urination)] (Kohli, 1994). This derivation of word is again substantiated when the clinical features of 'Prameha' are described as 'Prabhuta-mutrata' and 'Avil Mutrata' i.e. excessive urination with increased turbidity of urine. The whole description of diabetes from the etiology, pathogenesis, clinical features, complications and management all look to be comparable with the syndrome of diabetes mellitus as known in modern medicine.

The diabetes mellitus (DM) can be divided into three major subclasses i) type 1 diabetes mellitus, ii) type 2 diabetes mellitus and iii) Gestational diabetes, normally occurs during pregnancy may also lead to diabetes after delivery in some cases.

Type 1 diabetes mellitus:

Type 1 diabetes (previously known as insulin dependent diabetes mellitus; IDDM) is characterized by beta cell destruction by an autoimmune process usually leading to absolute insulin deficiency and acute onset, usually before 25 years of age (Jennifer Mayfield, 1998). Although the etiology is unknown, human leukocyte antigen association, viral factors and various environmental factors may contribute (Watkins and Sanders, 1995). Symptoms of type 1 diabetes usually develop over a short period, although beta cell destruction can begin years earlier. Symptoms may include increased thirst and urination, constant hunger, weight loss, blurred vision and extreme fatigue. If not diagnosed and treated with insulin, a person with type 1 diabetes can lapse into a life-threatening diabetic coma, also known as diabetic ketoacidosis.

Type 2 diabetes mellitus:

Type 2 diabetes mellitus (previously known as non-insulin dependent diabetes mellitus; NIDDM) is characterized by insulin resistance in peripheral tissue and insulin secretory defect of the beta cell (Jennifer Mayfield, 1998). This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. Defective beta cells become exhausted, further fueling the cycle of glucose intolerance and hyperglycemia. The etiology of type 2 diabetes mellitus is multifactorial and probably genetically based, but it also has strong behavioral components. The symptoms of type 2 diabetes develop gradually. Their onset is not as sudden as in type 1 diabetes. Symptoms may include fatigue, frequent urination increased thirst and hunger,

weight loss, blurred vision and slow healing of wounds or sores. Type 2 diabetes has strong genetic influences and occurs in identical twins with almost total concordance (Barnett *et al*., 1981; Leslin and Pyke, 1987). β cell mass is relatively well preserved but insulin secretions in response to specific secretogogues is reduced and clean evidence exists for resistance to insulin action in peripheral tissues (Gepts, 1984; DeFronzo, 1988; Savage *et al*., 1975; Porte, 1991). The plasma insulin level in type 2 diabetes patients are higher than or equal to that of non-diabetic control subjects (Yalow and Berson, 1960). This suggests that type 2 DM results from insulin resistance rather than insulin deficiency. However, it has become clear that both insulin resistance (Kahn, 1994) and insulin deficiency come in to play to cause hyperglycemia in type 2 DM patients. Abnormal regulation to glucose metabolism in the liver and impaired glucose tolerance was seen after an oral glucose load in type 2 DM subjects (Thorburn *et al*., 1995). Conditions associated with the development of insulin resistance, especially obesity and advancing age; greatly increase the risk of type 2 DM. Insulin resistance co-relates with certain patterns of obesity and is greater in individuals with central obesity than in those with more generalized obesity (Kissebah *et al*., 1982). Insulin resistance and hyperinsulinemia may also be associated with hypertension and hypertriglyceridemia, decreased-high density lipoprotein (HDL) cholesterol and increased risk of atherosclerosis and cardiovascular disease (Reaven, 1988; Karam, 1992).

Gestational diabetes

Some women develop gestational diabetes late in pregnancy, though this form of diabetes usually disappears after the birth of the baby. However, women who have had gestational diabetes have a 20-50 % chance of developing type 2 diabetes within 5 to 10 years. As with type 2 diabetes, gestational diabetes occurs more often in some ethnic groups and women with family history of diabetes. Gestational diabetes is caused by hormones of pregnancy or a shortage of insulin. Women with gestational diabetes may not experience any

symptoms. Infants of mother with gestational diabetes are vulnerable to several chemical imbalances such as low serum calcium and low serum magnesium levels but in general there are two major problems of gestational diabetes i) macrosomia and ii) hypoglycemia. For mother the complications like hypertension, pre-eclampsia and increased risk for developing type 2 diabetes mellitus and for baby macrosomia, hypoglycemia, jaundice, low calcium and magnesium respiratory distress syndrome, increased risk for childhood and adult obesity and risk for type 2 diabetes may occur (ADA, 2002)

Drugs treatment for diabetes mellitus:

Insulin:

Insulin is a hormone which helps to regulate blood sugar. A number of different types of insulin are available as medication, with some insulins acting for as long as a day and others acting for only a few hours. However, insulin is prescribed for people with type 1 diabetes and for people with type 2 diabetes who have not responded so well on oral medication (tablets). Insulin is the first line therapy for type-1 diabetes mellitus. There are different classification of Insulin like short acting, long acting, intermediate acting and rapid acting insulin. It is prescribed at 100-U i.e. 100 units per milli liter and 40 units per milli liter strengths. (Goodman & Gilman's, 2006)

Biguanides / Metformin

The only available diabetes medication in the biguanides class of drugs is metformin. Biguanides prevent the liver from producing glucose and helps to improve the body's sensitivity towards insulin. Metformin is commonly used as a first line treatment for type 2 diabetes and may occasionally be prescribed, in combination with insulin, for people with type 1 diabetes. Metformin was approved in 1994 (in the USA) and is prescribed as; 500mg tablets,850mg tablets, 500mg modified-release tablets, 750mg modified-release tablets, 1g

modified-release tablets, 1g oral powder sachets sugar free, 500mg oral powder sachets sugar free 500mg/5ml oral solution sugar free. (Goodman & Gilman's, 2006)

Sulphonylureas

Sulphonylureas are the class of antidiabetic drug for type 2 diabetes that tends to include those drugs which end in 'ide'. The following drugs are all in the sulphonylureas class (branded names in brackets): Glibenclamide –also known as Glyburide (Daonil), Glipizide (Glucotrol), Gliquidone (Glurenorm), Glyclopyramide (Deamelin-S), Glimepiride (Amaryl) Gliclazide (Diamicron), Sulphonylureas work by increasing the amount of insulin the pancreas produces and increasing the working effectiveness of insulin. The mode of action of sulphonylureas means that hypoglycemia and weight gain can be relatively common side effects. (Goodman & Gilman's, 2006)

Meglitinides / Prandial glucose regulator / Glinides

The glinides are a class of drug which have a similar response as sulphonylureas but act for a shorter time. Meglitinides are prescribed to be taken by people with type 2 diabetes within half an hour before eating. As the drugs act for a shorter period than sulphonylureas, the side effects of hypoglycemia and weight gain have a smaller likelihood. e.g Repaglinide (Prandin),Nateglinide (Starlix) (Goodman & Gilman's, 2006)

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors, such as acarbose (marketed as Precose or Glucobay) or miglitol (branded as Glyset) are drugs for type 2 diabetes which slow down the digestion of carbohydrates in the small intestine and therefore can help to reduce after meal blood sugar levels. (Goodman & Gilman's, 2006)

Thiazolidinedione / Glitazones

Thiazolidinediones, also known as glitazones, are a medication for type 2 diabetes which helps to improve insulin sensitivity and have been found to help decrease triglyceride levels. However, these have recently been in public spotlight as questions over their long term safety. In September 2010, the most popularly prescribed drug in this class rosiglitazone (Avandia) was banned for use by the European medicines Agency over heart attack concerns. Pioglitazone (Actos) has also made the news in connection with instances of bladder cancer, however, the danger has not been deemed sufficient to need to ban the drug in the UK. Pioglitazone works by making cells more sensitive to insulin, which is used to regulate the level of glucose in the body. Improving insulin sensitivity (or reducing insulin resistance) makes it easier for sugar (glucose) in the blood to get into the cells. Pioglitazone is administered orally with or without food. The drug is available in 15 mg, 30mg and 45mg tablet doses. Among older patients with diabetes, pioglitazone is associated with a significantly lower risk of heart failure and death than is rosiglitazone. Given that rosiglitazone lacks a distinct clinical advantage over pioglitazone, continued use of rosiglitazone may not be justified. (Goodman & Gilman's, 2006, Juurlink *et al*, 2009)

DPP-4 inhibitors / Gliptins

DPP-4 inhibitors, also known as gliptins, are a class of drug which help to stimulate the production of insulin and reduce the production of glucagon, particularly during digestion. DPP-4 inhibitors are usually prescribed for people with type 2 diabetes who have not responded well to drugs such as metformin and sulphonylureas. This drug class includes following medications (trade names in brackets): Sitagliptin (Januvia), Vildagliptin (Galvus), Saxagliptin (Onglyza), Linagliptin (Tradjenta) –approved for use in the USA. Sitagliptin works by inhibiting the DPP-4 enzyme that destroys GLP and GIP hormones, allowing both

to function more effectively. Both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released by the intestine and affect blood glucose levels. When more of these hormones are released blood sugar levels are reduced. It is available as 100mg tablets in the market. (Goodman & Gilman's, 2006)

Incretin mimetics / GLP-1 analogues

Incretin mimetics, also known as GLP-1 analogues, are an injectable treatment for type 2 diabetes. Incretin mimetics look to mimic the effect of a group of hormones called incretins which increase the production of insulin and decrease the release of glucagon in a relatively similar way DPP-4 inhibitors. This is not a coincidence as the way DPP-4 inhibitors work is to prevent the protein dipeptidyl peptidase-4 from destroying the incretin hormones. GLP-1 analogues have been found to be particularly effective in helping to improve blood glucose levels and helping with weight loss. The following GLP-1 analogues are prescribed in the UK (branded names in brackets): Exenatide (Byetta) and Liraglutide (Victoza). (Goodman & Gilman's, 2006)

Amylin analogues

Amylin is a hormone produced by the pancreas and released at the same time as insulin, but in much smaller quantities (about 1% compared with insulin). Amylin helps to suppress glucagon release and therefore reduce post meal blood glucose levels. Pramlintide acetate (marketed as Symlin) is available in the US as an injectable drug for the treatment of both type 1 and type 2 diabetes.The use of amylin with insulin can carry an increased chance of hypoglycemia. (Goodman & Gilman's, 2006)

3. AIMS AND OBJECTIVE

Aim of the study is to record and assess the adverse drug reactions during the treatment of diabetes mellitus in territory hospital.

The main objective of this study is to communicate the reported adverse reactions with through analysis (age wise, body weight wise, gender wise etc using WHO and Naranjo's analysis). These reports can act as an reference for future diabetic treatment with the label warning. All these exercise is expected to reduce the adverse drug reactions for future course of action.

4. PLAN OF WORK

The work was planned in such a way that to visit the Krishnagiri Government General hospital, Tamilnadu and meet the respective clinicians to get the information about the diabetes mellitus treatment by various classification of anti-diabetic drugs. It was also planned to interact with the patient or patient's attendant (who accompany the patient may be relative or friends) and record the adverse drug reactions including the symptoms and degree of severity of the adverse drug reaction encountered by them during the course of treatment. Along with severity of adverse drug reactions the patient counselling given by pharmacist, pharmacologist and clinicians to be recorded. These informations will also be collected from the interns, post graduate students, nurses. It was also planned to collect the respective bio-chemical analysis reports of the patients to know the severity of the disease progression, family history etc.

The work to be initiated from October, 2013 to December, 2013, i.e. close to three months for patient interaction and data collection. Next one month for assessment of the data collected using various causality assessment forms. Finally to prepare the report and share with regional pharmacovigilance centre.

5. METHODOLOGY

The study was conducted in Krishnagiri Government General Hospital, Tamilnadu.

STUDY PERIOD

This study which includes spontaneous prospective monitoring, reporting and documenting of ADRs of Diabetic patients undergoing various treatments was carried out for a period of 4 months (October, 2013 to January, 2014) by me on both in-patients and out-patients.

STUDY PROCEDURE

All the necessary and relevant data were collected from diabetes patients such as case notes, treatment charts, laboratory data reports, ADRs notification forms, with the help of patient's interview as well as reporter interview and the observations were recorded in ADR assessment form (*Note: since we do not administer any drug to the patients during the assessment period, there was no need for consent form*). The ward was visited almost daily during the study period and ADR assessment form were kept in the medication record with the aim that if any ADR alert is given in the ADR assessment form by the doctor or the nurses it will be noted and the data regarding ADR will be collected from patient record and were documented.

A suitable 'ADR reporting card' was designed based on the similar to the 'Blue Card' (Australian adverse drug reaction advisory committee) and 'Yellow Card' (UK

system of reporting ADRs) and was named as ‘Pink Card’ (Indian system of reporting ADRs) along with the necessary changes for the present study.

INCLUSION CRITERIA

- Both the type-1 and type-2 diabetes patients were included
- Both in-patients and out-patients were included in the study
- All the diabetic patients of different age groups were included.
- The physiological reaction of diabetic patients due to the drug alone were included
- Both male and female genders were included.
- Patients with diabetes along with cardiovascular disease, pulmonary infection and renal failure patients were also included.
- Patients taking all category medicines (diabetes drugs classification)
- The ADRs of all types were also included.

EXCLUSION CRITERIA

- The patients left the therapy without following medical advice (non compliance)
- The physiological reaction due to the disease (diabetes)
- Self-medication, prescriptions followed from non-qualified person.
- The ADRs due to other class of anti-diabetic drugs along with lipid lowering drugs like atorvastatin.
- The patients not willing to give consent for this study.
- The patients taking other system of medicine (siddha, ayurvedha, unani)

- The ADRs suspected due to co-administered drug used to treat other complications.
- The ADRs reported by patients on oral interview without any support of investigations.
- Allergic reaction due to pollens, dust and insects.

DOCUMENTATION OF ADRs

ADR monitoring form was designed and was implemented in the diabetic wards and also out-patient departments. If a suspected ADR was reported and had met the inclusion criteria, data on that particular suspected drug and reaction were collected and documented in a suitably designed ADR documentation form. Oral consent was taken from patients, their relatives (who accompany the patient for treatment) and concern doctors for further interviewing to collect data such as description of ADR and also permission to collect data.

All the relevant data which includes the drugs received by the patient prior to onset of reaction, their respective dosage, route of administration with frequency, date of onset of reaction and patient's allergy history were noted. The relevant date of drugs which were taken by patients prior to onset of reaction, like dosage, route of administration and its frequency were also recorded.

VARIOUS FORMS DESIGNED FOR DOCUMENTING ADR

- Notification of a suspected adverse drug reaction (ADR)

- Adverse drug reaction assessment form.
- Documentation form

ASSESSMENT OF ADRs

ADRs are assessed through Naranjo's causality assessment scale, new algorithm to identify the causality of ADRs, and WHO causality assessment scale. Depending on the questionnaire in the assessment form, ADRs were categorized as definite, probable, possible and unlikely. In case of Naranjo's, new algorithm scale and in the case of WHO probability scale depending on the questionnaire it was categorised as certain, probable, possible, unassessable/unclassified, unlikely, and conditional/unclassified.

The various forms for assessing ADRs were:

- Naranjo's causality assessment scale
- WHO causality scale
- New algorithm to identify the causality of ADRs

The questions present in the above forms were directy asked to the patients during the oral interview or it was recorded form the patient case sheets present in the ward during treatment. The cunsultation with concern doctor was also taken into consideration in relation to documentation of the ADRs.

PANEL OF JUDGES

The patient's case notes were reviewed independently by doctors and pharmacists and the panel of reviewers selected was consisted of 2 doctors of general medicine and 2 pharmacologists. The evaluation of the ADR monitoring and assessing causality was done by this panel. During the ward rounds if the physician required the consultation of other members of the health care team then it was also taken into consideration and on certain occasions the pharmacist's suggestions were recommended.

The recommendations were as follows:

- Prevision of drug information relevant to the suspected ADRs to the notifying doctor as a part of primary patient care.
- Educate the patient about the event of ADRs and prevention of further reactions recommendation of alternative therapy and identification of drug reaction.
- "Systems error" and drug allergy.

REPORTING ADRs TO NATIONAL PHARMACOVIGILANCE CENTRE

The data regarding ADRs were collected and documented from the patient medication history, patient case notes, treatment charts, laboratory data reports, patient interview, and patient reporter interview. The data collected will be reported to national pharmacovigilance centre through peripheral pharmacovigilance centre.

6. RESULTS AND DISCUSSION

6.0 RESULTS

The study was performed among the diabetes mellitus patients visited to the endocrine (diabetology) centre of territory hospitals and diabetic care clinics. The study was conducted for suspected ADRs in 118 patients. Among 118 patients, 14 patients were excluded from the study due to not following the medical advice, left the therapy without medical advice, patients shifted to other diabetes care clinics due to convenient of the patients so finally the 104 ADRs of diabetes mellitus treatment was evaluated and reported.

Out of 104 ADRs, the in- patients were 40 (38%) and the out patients were 64 (62%) (Table 6.1 & Figure 6.1). The sex wise distribution of diabetes mellitus patients showed that the male in patients and out patients numbers were 20 (42%), 28 (58%) respectively whereas in the case of females it was 26 (46%) for in patients and 30 (54%) for out- patients. It was observed that the out-patients were more suspected for ADRs in diabetes mellitus (Table 6.2 & Figure 6.2)

Table: 6.1

The incidence of ADRs in male and female patients

S.No	Gender	No. of ADRs	Percentage
1	Male	48	46.15
2	Female	56	53.85

Figure: 6.1

The incidence of ADRs in male and female patients

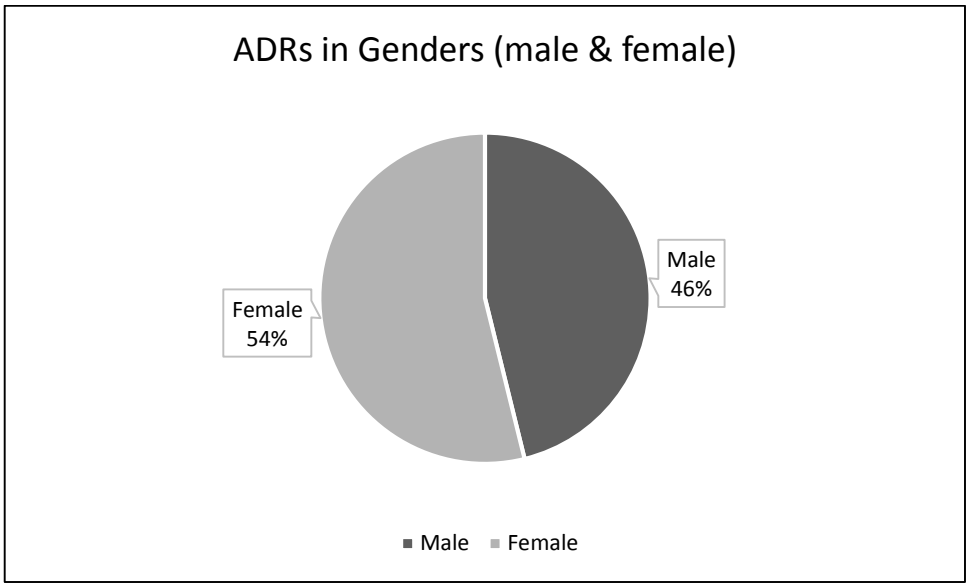


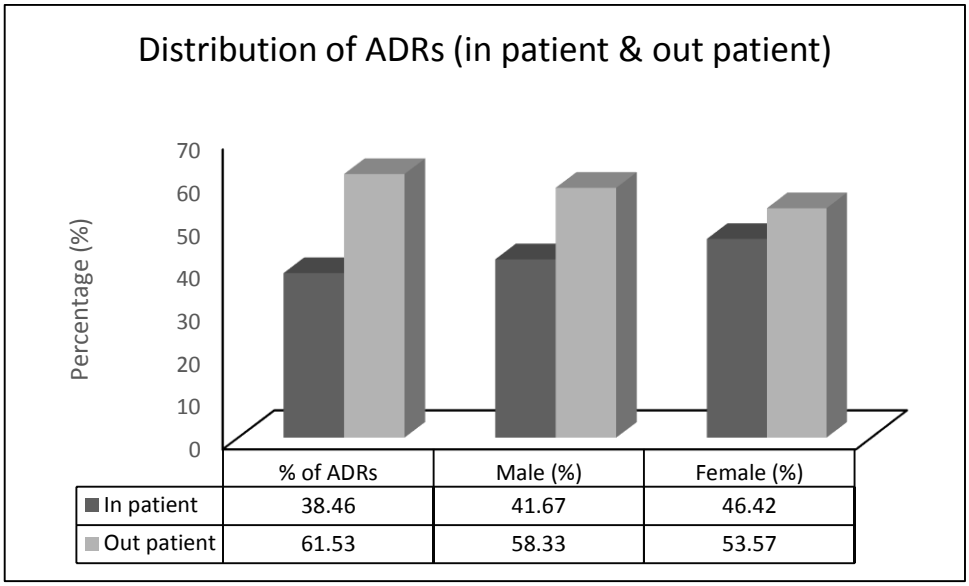
Table 6.2

Distribution of ADRs in both in-patients and out-patients

S.No	Types of ADRs	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	In patient	40	38.46	20	41.67	26	46.42
2	Out patient	64	61.53	28	58.33	30	53.57

Figure: 6.2

Distribution of ADRs in both in-patients and out-patients (gender wise)



	% of ADRs	Male (%)	Female (%)
In patient	38.46	41.67	46.42
Out patient	61.53	58.33	53.57

6.1 WEIGHT DISTRIBUTION

The maximum ADRs were found in the weight group of 61 kg or above and in this weight group 60 (60%) patients were reported ADRs amongst which 28 (58%) were male and 34 (61%) were female. In the weight group of 0-20 the number of ADRs were 3(3%) in which 2(4%) were male and 1(2%) were female respectively. The weight group of 21-40 the ADRs were reported 7(7%) amongst which 3(6%) were male and 4 (7%) were female. Further, 41-60 weight group is the second dominated weight group had 32(31%) of ADRs in which male were 15(31%) as well as female were 17(30%) respectively (Table 6.3 & Figure 6.3)

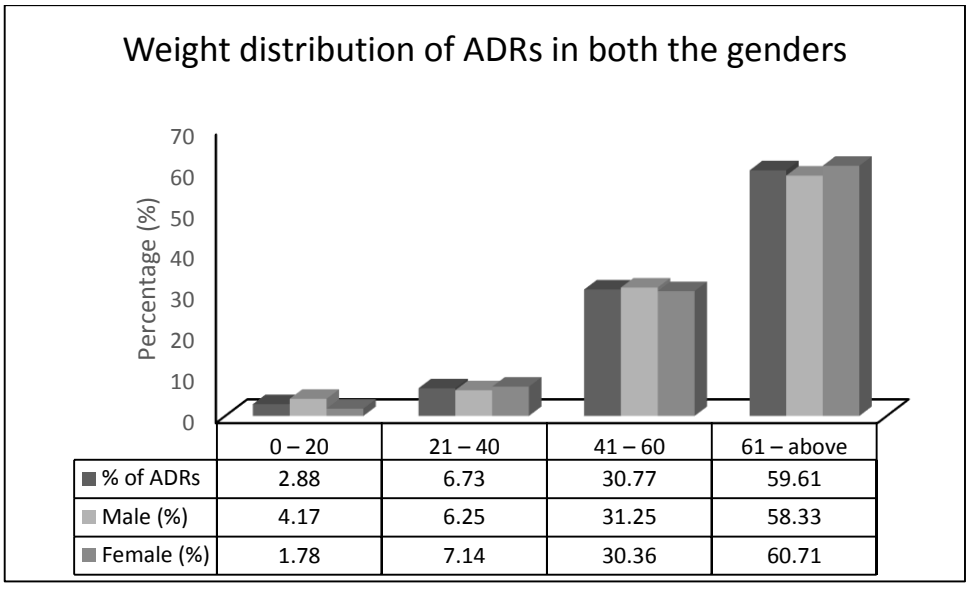
Table: 6.3

Weight distribution of ADRs in both the genders

S.No	Weight (in Kg)	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	0 – 20	3	2.88	2	4.17	1	1.78
2	21 – 40	7	6.73	3	6.25	4	7.14
3	41 – 60	32	30.77	15	31.25	17	30.36
4	61 – above	62	59.61	28	58.33	34	60.71

Figure: 6.3

Weight distribution of ADRs in both the genders



6.2 AGE DISTRIBUTION

The suspected ADRs individual were categorized in to different group wise <=10,10-20,20-30,30-40,40-50and >=50. The age group of 30-40 reported highest numbers of ADRs 42(40%), in which the male patients were 19(40%) and the female number of patients were 23(41%). The second dominant age group were 40-50 in this 20(19%) of patients reported ADRs and the number of ADRs were 9 (19%) in male and the number of ADRs were 11 (20%) female. The third place of highest ADRs numbers found in the age group of 20-30 where 8 (17%) were male patients and the number of ADRs were 18(17%) whereas the female number of ADRs were 10 (18%). Further the age group of >=50 were shows a total 17 (16%) ADRs amongst which the male patients were 8 (17%) and the female patients were 9 (16%). The age group of <=10 shows 3(3%) of ADRs in which the male number of ADRs were 2 (4%) and the female number of ADRs 1(2%). The age group of 10-20 were reported with ADRs of 4(4%) along with almost equal representation of male and female contribution 2(4%), 2(4%) respectively (Table 6.4 & Figure 6.4). Table 6.5 represents the Age wise contribution of male and female patients.

Table: 6.4

Age wise distribution of ADRs in both the genders

S.No	Age (years)	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	<10	3	2.88	2	4.17	1	1.78
2	10 – 20	4	3.85	2	4.17	2	3.57
3	20 – 30	18	17.31	8	16.67	10	17.86
4	30 – 40	42	40.38	19	39.58	23	41.07
5	40 – 50	20	19.23	9	18.75	11	19.64
6	>50	17	16.35	8	16.67	9	16.07

Figure: 6.4

Age wise distribution of ADRs in both the genders

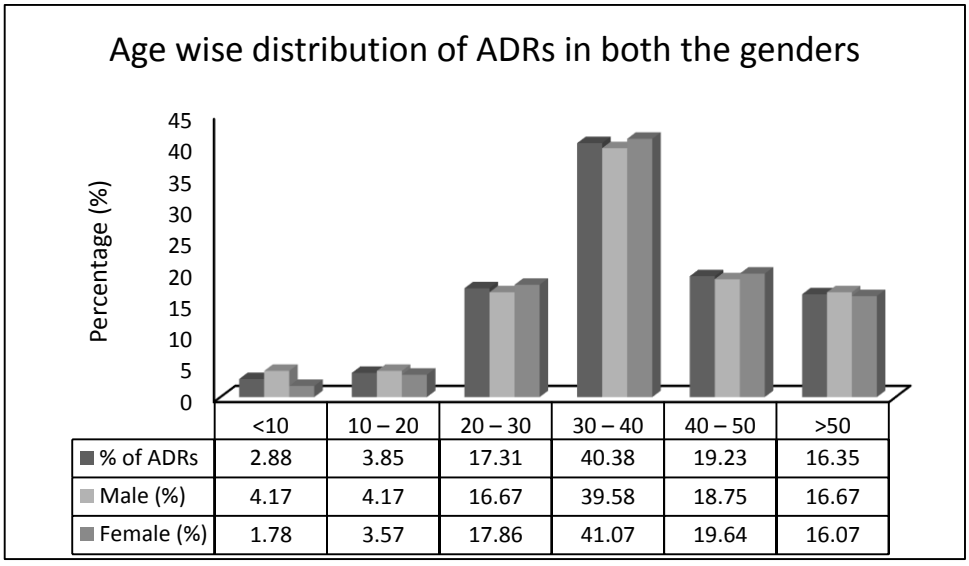


Table: 6.5

Table showing the age wise percentage contribution of ADRs

Age (years)	**Male** (Percentage; %)	**Female** (Percentage; %)	**Total** (Percentage; %)
<10	**2** (66.67)	**1** (33.33)	**3** (100.0)
10 – 20	**2** (50.0)	**2** (50.0)	**4** (100.0)
20 – 30	**8** (44.44)	**10** (55.56)	**18** (100.0)
30 – 40	**19** (45.24)	**23** (54.76)	**42** (100.0)
40 -50	**9** (45.0)	**11** (55.0)	**20** (100.0)
>50	**8** (47.06)	**9** (52.94	**17** (100.0)
Total	**48** (46.15)	**56** (53.85)	**104** (100.0)

6.3. 95% CONFIDENCE INTERVALS OF AGE & WEIGHT

The 95% confidence intervals of age showed 33.95 to 38.10 and at the same time the confidence interval of weight showed 55.7 to 61.01. The mean of age was 36.03 and the standard error of mean was 1.04 and at the same time the mean weight of 104 patients was 58.39 and the standard error of mean was 1.32 (Table 6.6 & Figure 6.5).

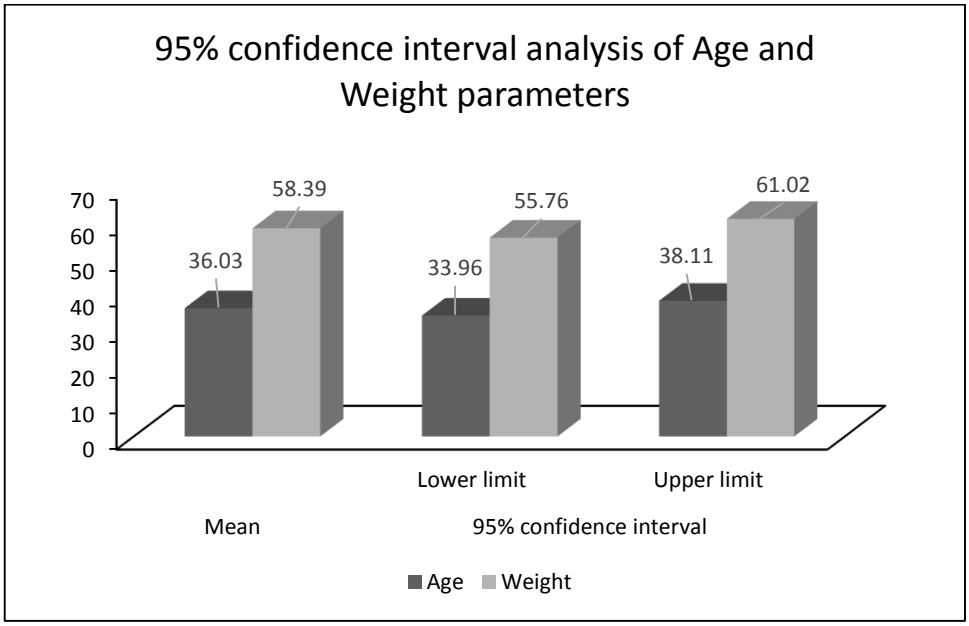
Table: 6.6

Table showing 95% confidence intervals of age and weight

Variable	Observation	Mean	Std. Err.	95% confidence interval	
Age	104	36.03	1.044	33.9584	38.1061
Weight	104	58.39	1.32	55.7567	61.0175

Figure: 6.5

Figure showing 95% confidence interval analysis of Age and Weight parameters



6.4 STATISTICAL ANALYSIS OF AGE AND WEIGHT

The standard deviation of age and weight were 10.06 and 12.77 respectively and the median of age and weight was 36 and 62 respectively (Table 6.7 & Figure 6.6).

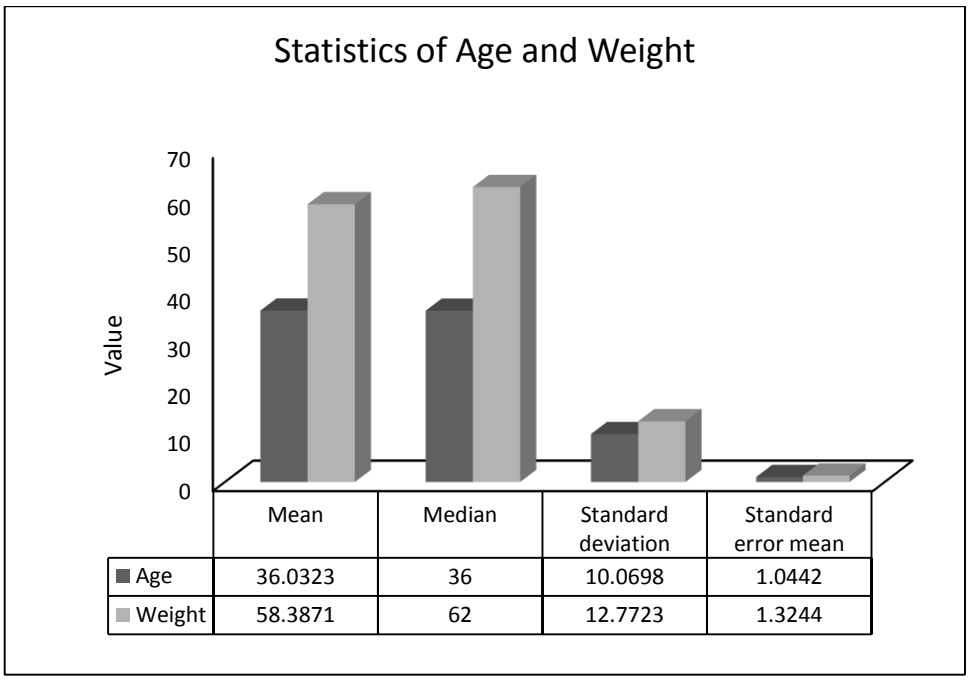
Table: 6.7

Table showing the Statistics of age and weight

Statistics	Age	Weight
Mean	36.0323	58.3871
Median	36	62
Standard deviation	10.0698	12.7723
Standard error mean	1.0442	1.3244

Figure: 6.6

Figure showing the Statistics of Age and Weight



6.5 MANAGEMENT OF ADRs

The ADRs managed in the study area was done in 3 ways, they are withdrawn the drug, just altering the dose of the drug, and by no change in the diabetes mellitus. From the reported ADRs the management step taken by withdrawing the drug from 52 (50%) patients in which male were 25 (52%) and the female were 27 (48%). The drug dose altered patients were 6 (6%) in which the male patients were 2 (4%) and the female patients was 4 (7%). The unaltered therapy was observed in total 46 (44%) patients amongst which the male were 21 (44%) and the female were 25 (45%) (Table 6.8 & Figure 6.7)

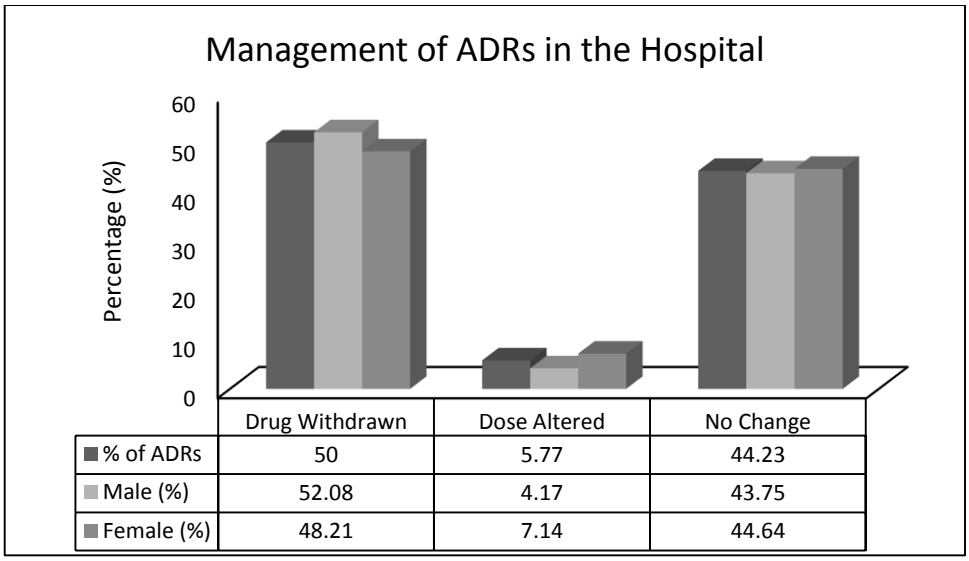
Table: 6.8

Management of ADRs in the Hospital

S.No	Management	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	Drug Withdrawn	52	50.0	25	52.08	27	48.21
2	Dose Altered	6	5.77	2	4.17	4	7.14
3	No Change	46	44.23	21	43.75	25	44.64

Figure: 6.7

Management of ADRs in the Hospital



6.6 SEVERITY OF REPORTED ADRs

The severity of ADRs from the reported patients were mild 16 (15%), moderate 77 (74%), severe 9 (9%) and the lethal was 2(2%). The ADRs were dominant in the moderate class whereas mild class shows the second place (Table 6.9& Figure 6.8).

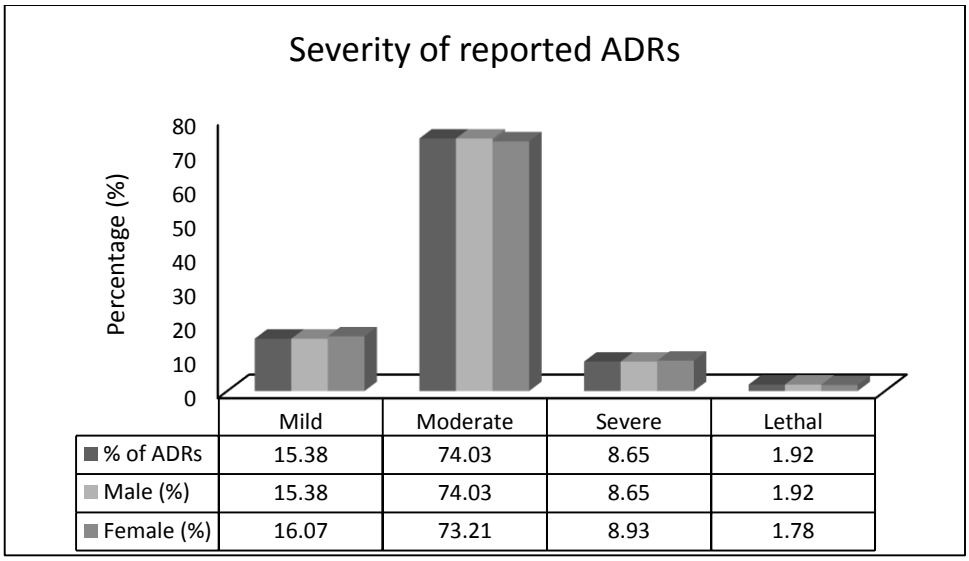
Table: 6.9

Table showing severity of reported ADRs

S.No	Severity	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	Mild	16	15.38	7	14.58	9	16.07
2	Moderate	77	74.03	36	75.0	41	73.21
3	Severe	9	8.65	4	8.33	5	8.93
4	Lethal	2	1.92	1	2.08	1	1.78

Figure: 6.8

Figure showing severity of reported ADRs



	Mild	Moderate	Severe	Lethal
% of ADRs	15.38	74.03	8.65	1.92
Male (%)	15.38	74.03	8.65	1.92
Female (%)	16.07	73.21	8.93	1.78

6.7 NARANJO'S CAUSALITY ASSESSMENT OF ADRs

From the reported ADRs of 104 patients the Naranjo's causality assessment shows the 'definite' number of ADRs were 54 (52%) in which the male patients ADRs were 25 (52%) and the female patients ADRs were 29 (52%). The scale 'probable' number of ADRs were 36 (35%) in which male were 17 (35%) and the female were 19 (34%). The 'possible' was reported with 10 (10%) patients in which male patients were 4 (8%) and the female patients were 6 (11%). The 'unlikely' reported was in only 4 (4%) patients in which male patients were 2 (4%) and the female patients were 2 (4%) respectively (Table 6.10 & Figure 6.9).

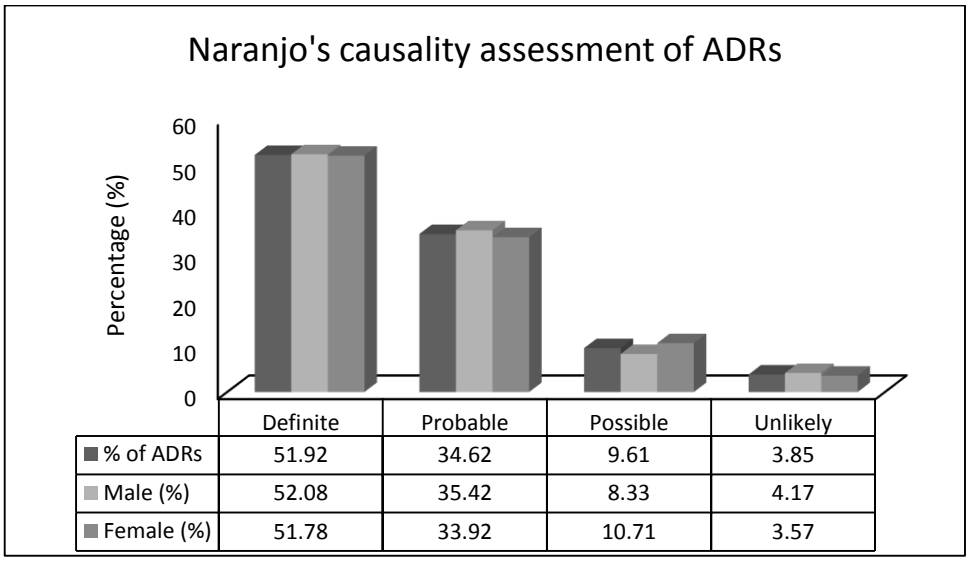
Table: 6.10

Table showing Naranjo's causality assessment of ADRs

S.No	Causality	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	Definite	54	51.92	25	52.08	29	51.78
2	Probable	36	34.62	17	35.42	19	33.92
3	Possible	10	9.61	4	8.33	6	10.71
4	Unlikely	4	3.85	2	4.17	2	3.57

Figure: 6.9

Figure showing Naranjo's causality assessment of ADRs



6.8. WHO PROBABILITY ASSESSMENT OF ADRs

The ADRs assessed by WHO probability scale showed the results and 65 (63%) patients were in 'certain' group which includes 31 (65%) of male patients and 34 (61%) of female patients. The 'probable' was observed in 27 (26%) of patients in which the 12 (25%) were male patients and 15 (27%) were females patients. The 'possible' were reported with 4 (4%) patients in which the male patient were 2 (4%) and the female patients were 2 (4%). The 'Unclassified / unassessable was reported with 5 (5%) patients and amongst these the male and female patients were 2 (4%), 3 (5%) respectively. The 'unlikely' was reported with 2 (1.9%) in which male 1 (2%) and female 1 (1.8%). Finally, conditional/un-classified was reported with 1 ADR which contributes 0.96% in which no male and 1 (1.8%) female contribution was there. (Table 6.11 & Figure 6.10)

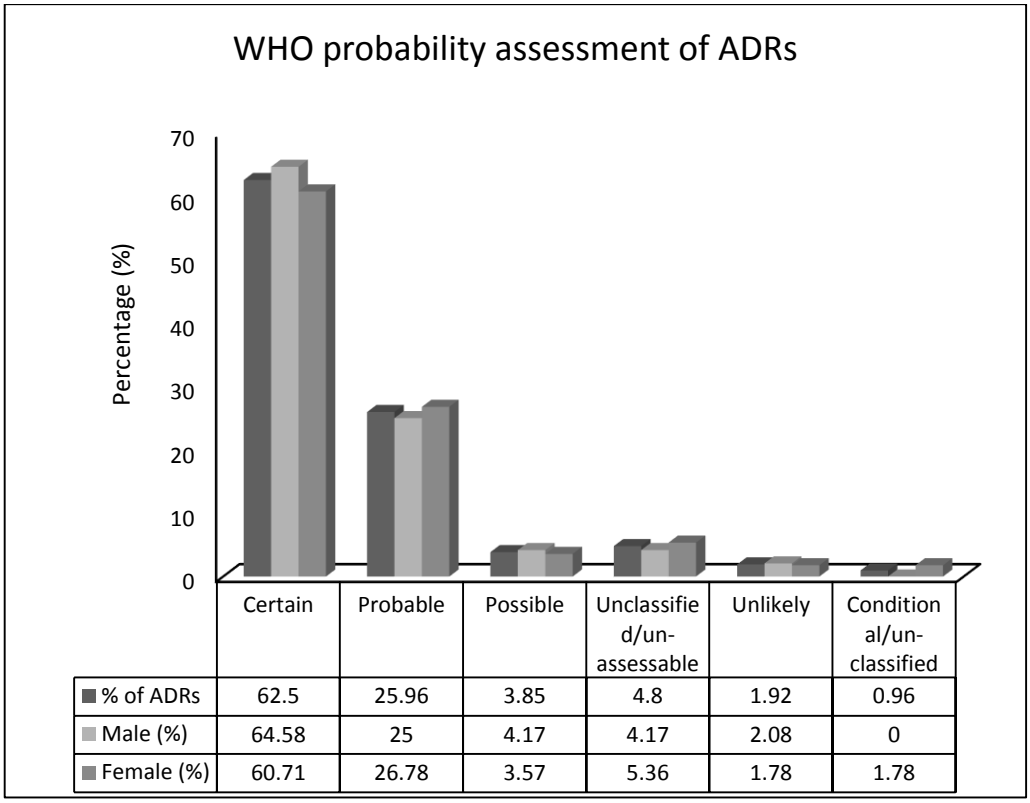
Table: 6.11

Table showing WHO probability assessment of ADRs

S.No	WHO probability	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	Certain	65	62.50	31	64.58	34	60.71
2	Probable	27	25.96	12	25.00	15	26.78
3	Possible	4	3.85	2	4.17	2	3.57
4	Unclassified/un-assessable	5	4.80	2	4.17	3	5.36
5	Unlikely	2	1.92	1	2.08	1	1.78
6	Conditional/un-classified	1	0.96	0	0.0	1	1.78

Figure: 6.10

Figure showing WHO probability assessment of ADRs



	Certain	Probable	Possible	Unclassified/un-assessable	Unlikely	Conditional/un-classified
% of ADRs	62.5	25.96	3.85	4.8	1.92	0.96
Male (%)	64.58	25	4.17	4.17	2.08	0
Female (%)	60.71	26.78	3.57	5.36	1.78	1.78

6.9 ASSESSMENT OF ADRs THROUGH NEW ALGORITHM

The new algorithm shows 'possible' was the highest number 48 (46%) in which the males were 22 (46%) and the females were 26 (46.4%). The 'probable' shows the second highest with 38 (37%) patients and group the males were 17 (35.4%) female's were 21 (38%). The 'definite' shows 16 (15%) patients and amongst these the males were 8 (17%) and the females were 8 (14%). In the 'unlikely' group, a total reported ADRs was 2 (1.9%) amongst which the males were 1 (2%) and females were 1 (1.8%) respectively (Table 6.12 & Figure 6.11).

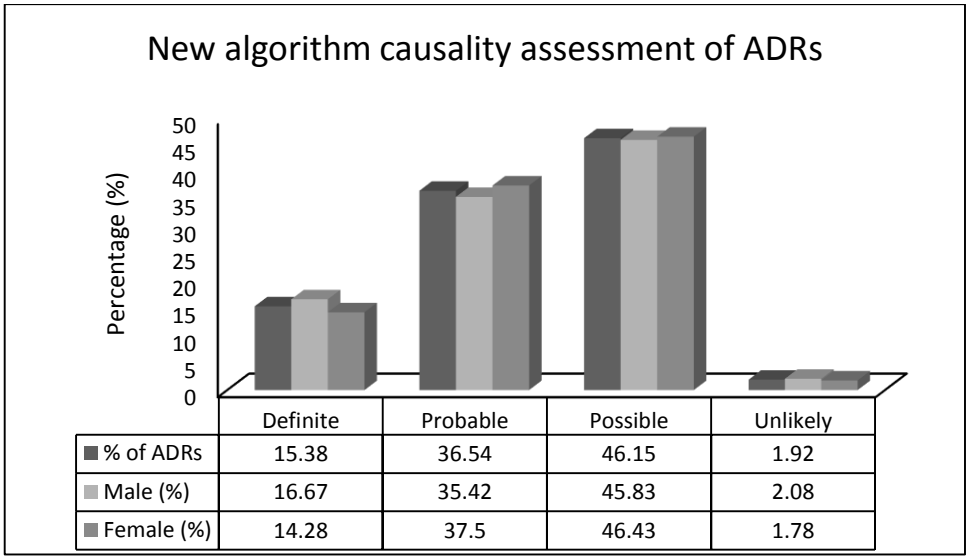
Table: 6.12

Table showing assessment of ADRs through new algorithm

S.No	New algorithm (Causality)	Number of ADRs	% of ADRs	Sex Distribution			
				Male	%	Female	%
1	Definite	16	15.38	8	16.67	8	14.28
2	Probable	38	36.54	17	35.42	21	37.50
3	Possible	48	46.15	22	45.83	26	46.43
4	Unlikely	2	1.92	1	2.08	1	1.78

Figure: 6.11

Figure showing assessment of ADRs through new algorithm



6.10 THE DRUG AND ADRs RATIO

The highest rate of ADRs were reported in 'Insulin' 34 (33%) treated patients whereas the second highest ADRs was associated with 'Metformin' 28 (27%). The number of patients were present in the 'Gliclazide' was 19 (18.3%). The 'Pioglitazone' reported with 15 (14.4%) of patients and the 'Sitagliptin'reported with 8 (7.7%) patients (Table 6.13 & Figure 6.12). Table 6.14 represents the reported adverse drug reactions for diabetes mellitus treatment classification.

Table: 6.13

Table showing the drugs and ADRs ratio

S.No	Drugs	Number of ADRs	Percentage
1	Metformin	28	26.92
2	Gliclazide	19	18.27
3	Insulin	34	32.69
4	Pioglitazone	15	14.42
5	Sitagliptin	8	7.69
6	Total	104	100.0

Figure: 6.12

Figure showing the drugs and ADRs ratio

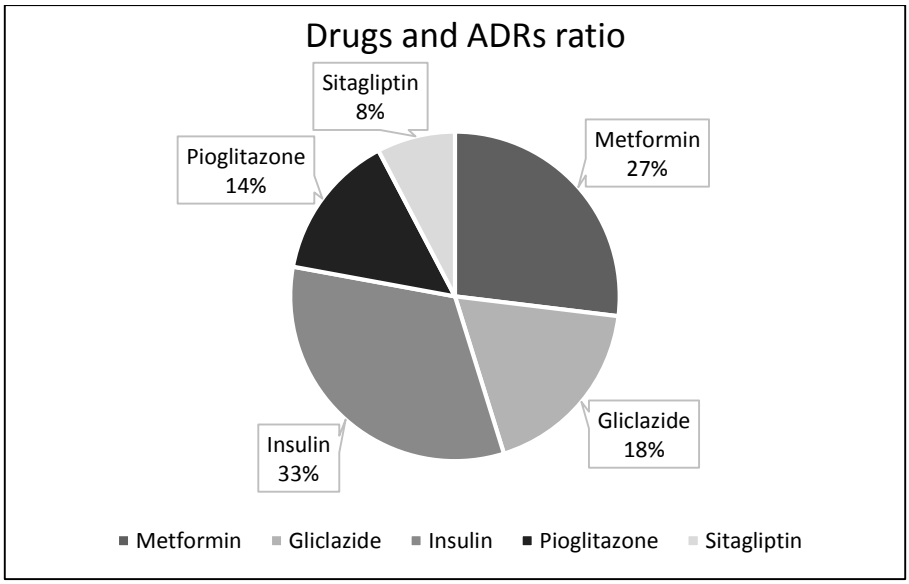


Table: 6.14

Table showing reported adverse drug reactions

S.No.	Suspected major ADRs	Number of ADRs	Percentage
1	Diarrhea	29	27.88
2	Nausia/Vomiting	4	3.85
3	Flatulence	4	3.85
4	Asthenia	3	2.88
5	Indigestion	2	1.92
6	Abdominal discomfort	2	1.92
7	Headache	4	3.85
8	Lactic acidosis	2	1.92
9	Renal impairment	2	1.92
10	Hypoglycemia	4	3.85
11	Rash/Erythemia	1	0.96
12	Taste disorder	1	0.96
13	Sweating	1	0.96
14	Palpitation	1	0.96
15	Hypertension	4	3.85
16	Impaired Hepatic functions	4	3.85
17	Dehydration	2	1.92
18	Hyperkalaemia	1	0.96
19	Malaise	1	0.96
20	Urinary incontinence	3	2.88
21	Hyponatraemia	2	1.92
22	pancreatitis	4	3.85
23	Anuria	1	0.96
24	Dyspepsia	1	0.96
25	Hypothermia	2	1.92
26	Pyrexia	2	1.92
27	Oedema peripheral	3	2.88
28	Haemolytic Anaemia	1	0.96
29	Dyspnoea	1	0.96
30	Face oedema	1	0.96
31	Dizziness	1	0.96
32	Fatigue	2	1.92
33	Vision problems	1	0.96
34	Weight gain	5	4.81
35	Congestive heart failure	2	1.92

6.11 REPORTED ADRs OF METFORMIN

The highest number of Metformin treated patients reported with diarrhea (21.4%) and the second AE was nausea/vomiting and the number of patients were 2 (7.4%). Along with this nausea/vomiting equal number of cases were reported for the following adverse events i.e. Flatulence, Headache, Renal impairment, Taste disorder and Impaired Hepatic functions. These AE were accounted for 2 patients each contributing with 7.4%. The third most reported AE were Asthenia, Indigestion, Abdominal discomfort, Lactic acidosis, Hypoglycemia, Rash, Palpitation and Dehydration. They contribute each 1 patient which accounts for 3.57% each to the AE. (Table 6.15 & Figure 6.13)

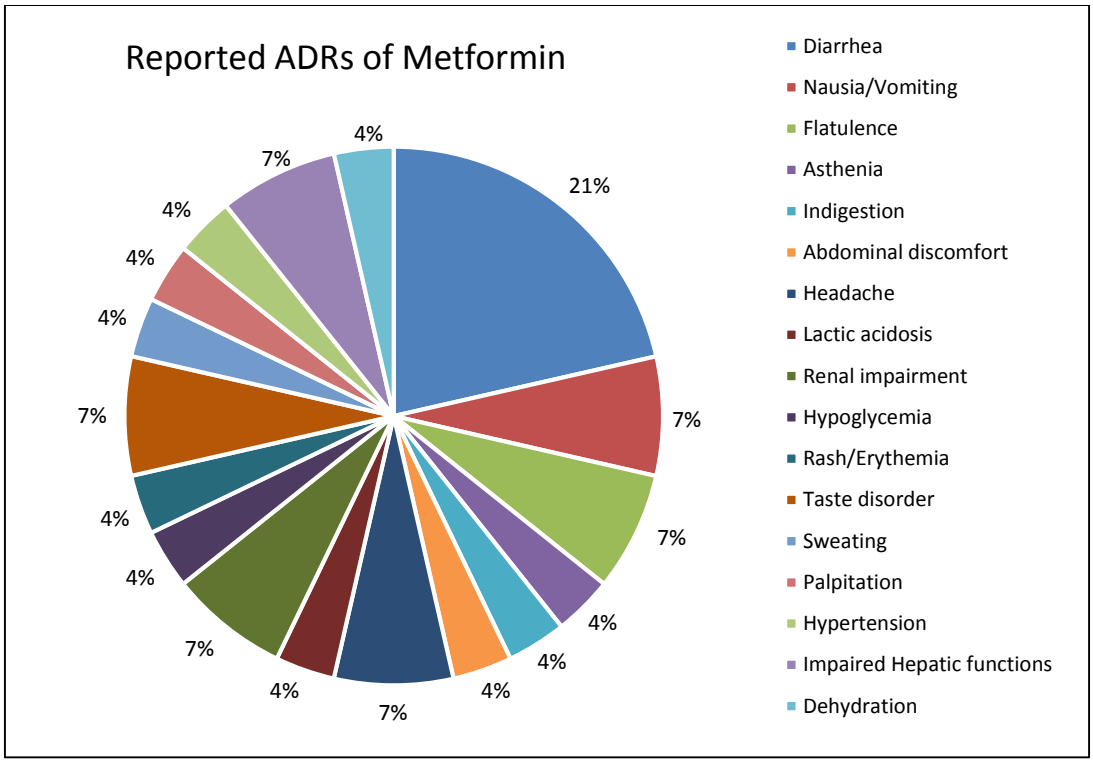
Table: 6.15

Table showing Reported ADRs of Metformin

S.No.	Suspected major ADRs	Number of ADRs	Percentage
1	Diarrhea	6	21.43
2	Nausia/Vomiting	2	7.14
3	Flatulence	2	7.14
4	Asthenia	1	3.57
5	Indigestion	1	3.57
6	Abdominal discomfort	1	3.57
7	Headache	2	7.14
8	Lactic acidosis	1	3.57
9	Renal impairment	2	7.14
10	Hypoglycemia	1	3.57
11	Rash/Erythemia	1	3.57
12	Taste disorder	2	7.14
13	Sweating	1	3.57
14	Palpitation	1	3.57
15	Hypertension	1	3.57
16	Impaired Hepatic functions	2	7.14
17	Dehydration	1	3.57

Figure: 6.13

Figure showing reported ADRs of Metformin



6.12 REPORTED ADRs OF GLICLAZIDE

The Gliclazide treated patients reported highest number of AE with pancreatitis 3 (15.8%) and the Headache, Renal impairment, Hypoglycemia, Impaired hepatic functions and weight gain were seen with 2 (10.5%) of the Gliclazide treatment, whereas, the Nausia/vomiting, Abdominal discomfort, Hypertension, Peripheral Oedema, and Congestive heart failure reported with 1 (5.3%) patients each (Table 6.16 & Figure 6.14)

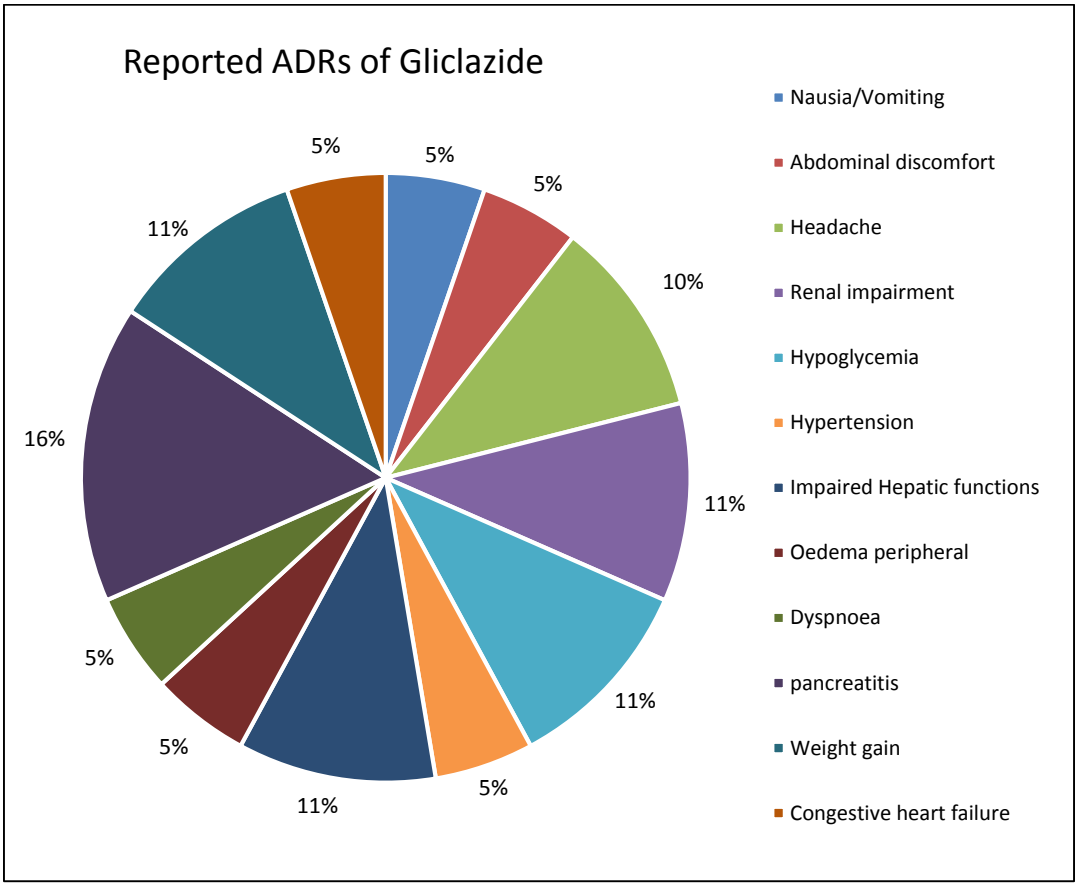
Table: 6.16

Table showing reported ADRs of Gliclazide

S.No.	Suspected major ADRs	Number of ADRs	Percentage
1	Nausia/Vomiting	1	5.26
2	Abdominal discomfort	1	5.26
3	Headache	2	10.53
4	Renal impairment	2	10.53
5	Hypoglycemia	2	10.53
6	Hypertension	1	5.26
7	Impaired Hepatic functions	2	10.53
8	Oedema peripheral	1	5.26
9	Dyspnoea	1	5.26
10	pancreatitis	3	15.79
11	Weight gain	2	10.53
12	Congestive heart failure	1	5.26

Figure: 6.14

Figure showing reported ADRs of Gliclazide



6.13 REPORTED ADRs OF INSULIN

The Insulin reported the highest AE in the form of Hypoglycemia amongst 5 (14.7%) patients whereas the second highest AE was with Fatigue, Weight gain, Headache, Dyspnoea and Peripheral Oedema which accounts for 8.8% with 3 patients of each AE. The Nausia, Lactic acidosis, Hyponatraemia and Impaired Hepatic functions accounts for 2 patients each which contributes to 5.9% each of the AE. Apart from the mentioned AEs minor AEs like Dizziness, Hypertension, and Congestive Heart failure were accounting for 3% each with 1 patient each of the AE. (Table 6.17& Figure 6.15)

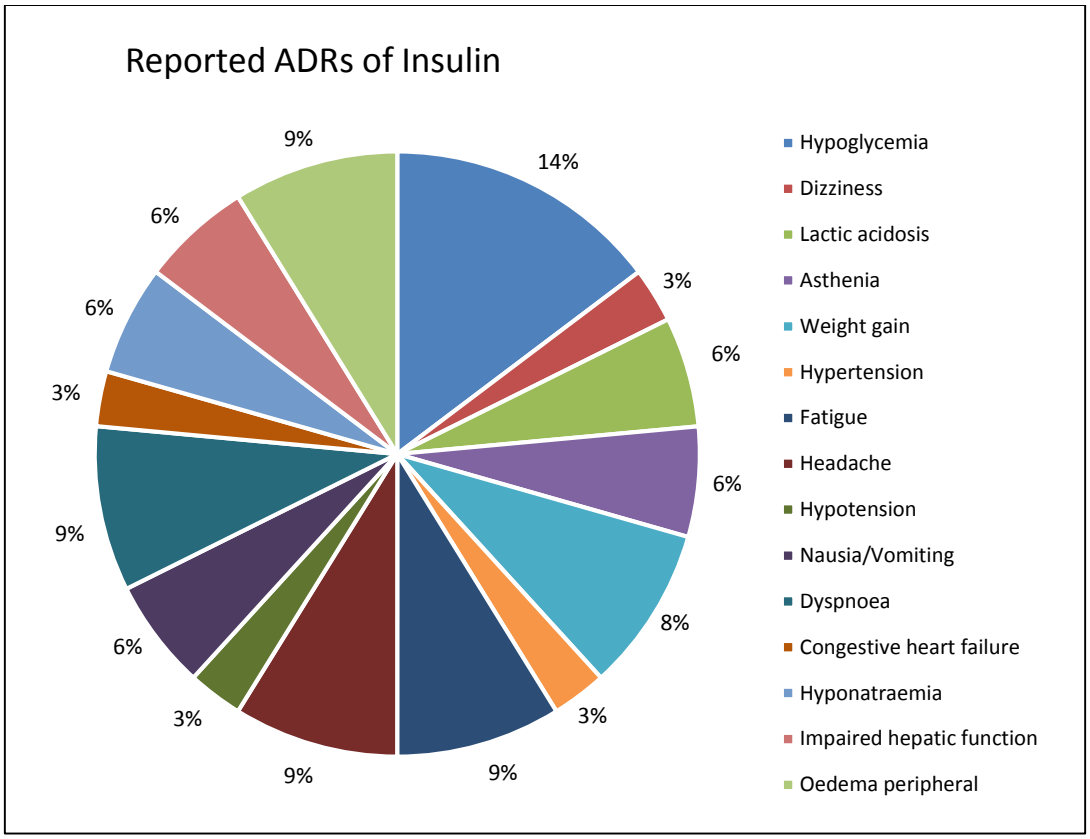
Table: 6.17

Table showing reported ADRs of Insulin

S.No.	Suspected major ADRs	Number of ADRs	Percentage
1	Hypoglycemia	5	14.71
2	Dizziness	1	2.94
3	Lactic acidosis	2	5.88
4	Asthenia	2	5.88
5	Weight gain	3	8.82
6	Hypertension	1	2.94
7	Fatigue	3	8.82
8	Headache	3	8.82
9	Hypotension	1	2.94
10	Nausia/Vomiting	2	5.88
11	Dyspnoea	3	8.82
12	Congestive heart failure	1	2.94
13	Hyponatraemia	2	5.88
14	Impaired hepatic function	2	5.88
15	Oedema peripheral	3	8.82

Figure: 6.15

Figure showing reported ADRs of Insulin



6.14 REPORTED ADRs OF PIOGLITAZONE

In the Pioglitazone treated patients the highest number of AEs reported were Weight gain, Impaired Hepatic functions, Hypglycemia and Pancreatitis with 2 patients each which contributes to 13.3% of AEs. Minor AEs like, nausea, Abdominal discomfort, Vision problems and Oedema contributes 6.7% each with 1 patient each from the assessment group. (Table 6.18 & Figure 6.16)

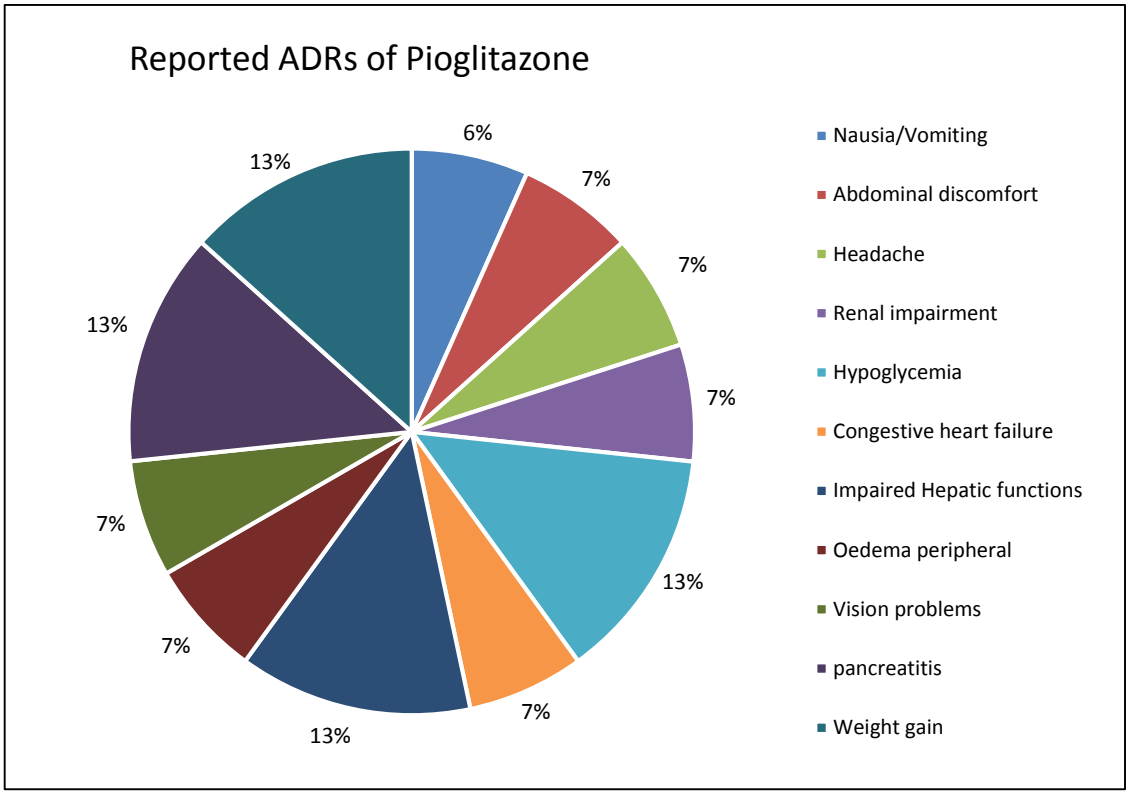
Table: 6.18

Table showing reported ADRs of Pioglitazone

S.No.	Suspected major ADRs	Number of ADRs	Percentage
1	Nausia/Vomiting	1	6.67
2	Abdominal discomfort	1	6.67
3	Headache	1	6.67
4	Renal impairment	1	6.67
5	Hypoglycemia	2	13.33
6	Congestive heart failure	1	6.67
7	Impaired Hepatic functions	2	13.33
8	Oedema peripheral	1	6.67
9	Vision problems	1	6.67
10	pancreatitis	2	13.33
11	Weight gain	2	13.33

Figure: 6.16

Figure showing reported ADRs of Pioglitazone



6.15 REPORTED ADRS OF SITAGLIPTIN

Pancreatitis and Impaired Hepatic functions were reported as major AE of Sitagliptin treatment which contributes 25% with 2 patients of each AE. Minor AEs like Headache, Renal impairment, Hypoglycemia and Erythemia accounts for 12.5% each with 1 patient of each AE from the assessment group was reported. (Table 6.19 & Figure 6.17)

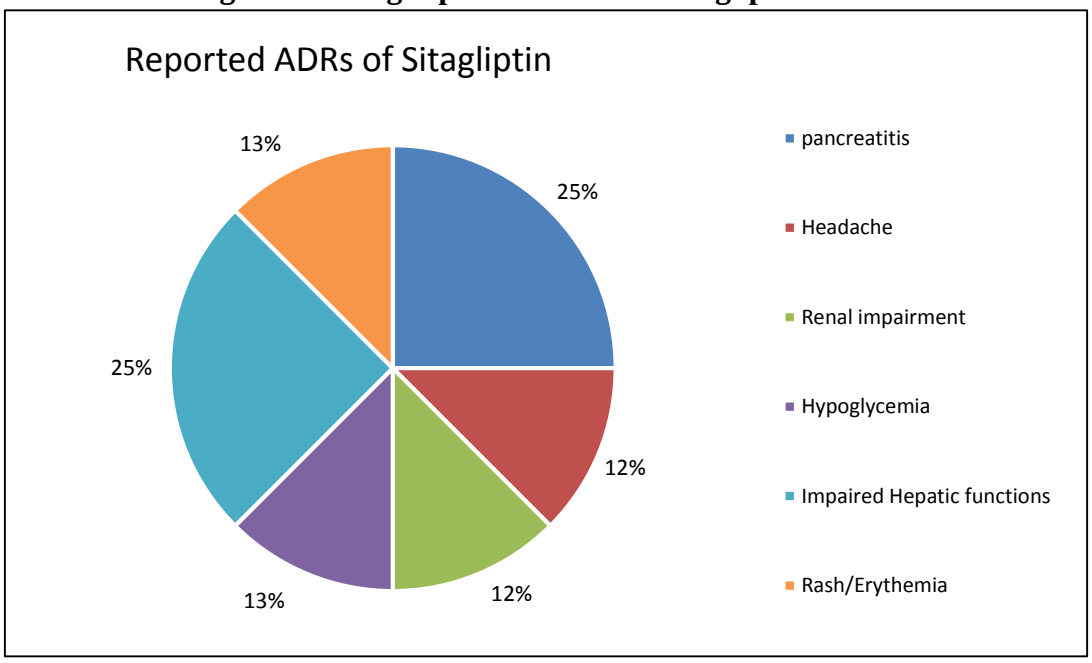
Table: 6.19

Table showing the reported ADRs of Sitagliptin

S.No.	Suspected major ADRs	Number of ADRs	Percentage
1	pancreatitis	2	25.0
2	Headache	1	12.5
3	Renal impairment	1	12.5
4	Hypoglycemia	1	12.5
5	Impaired Hepatic functions	2	25.0
6	Rash/Erythemia	1	12.5

Figure: 6.17

Figure showing reported ADRs of Sitagliptin



6.16 SIGNIFICANCE OF CAUSALITY ASSESSMENT

With a view to observe the level of significance a test was done known as "Kappa test for agreement". These observations suggest that a significant agreement between New Algorithm and Naranjo's Scales was found along with the Kappa value is 0.702 i.e. 70.2% (Table 6.20.1 & 6.20.2).

Table: 6.20.1

A Significant agreement between New Algorithm & Naranjo's

New Algorithm	Naranjo's causality				Total
	Possible	Definite	Probable	Unlikely	
Possible	5	40	3	0	48
Definite	1	10	4	0	15
Probable	2	6	28	0	36
Unlikely	1	0	2	2	5
Total	9	56	37	2	104

Table: 6.20.2

Kappa test for agreement

Measure of Kappa	Value	Asymp std error (a)	Approx T (b)	Approx .(sig)
	0.702	0.0576	5.834	0.00

(a) Not assuming the null hypothesis

(b) Using the asymptotic standard error assuming the null hypothesis

6.17 HIERARCHICAL CLUSTER ANALYSIS

The Hierarchical cluster analysis were showing that there was no significance of Age, sex, body weight with ADRs this observations suggest that the ADRs were not dependent of Age, sex and body weight of the patients

6.18. DISCUSSION

India has more than half a million qualified Doctors and 15,000 hospitals having bed strength of 6.24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in our country. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs (Ghosh, *et al*., 2011). The US FDA has released a safety warning against rosiglitazone, a drug approved to treat Type 2 diabetes mellitus. An analysis by prominent cardiologist Steven Nissen, published his clinical trial results related to adverse drug reactions of rosiglitazone. It suggests that 43% of the population (from the trial subjects) have a chance of suffering a heart attack (Nissen and Wolski., 2007).

During 1999, the popular pain killer rofecoxib (Vioxx) was launched by Merck had serious adverse effects on cardiovascular system such as heart attack and stroke. This was testified by FDA whistle blower and finally the pain killer rofecoxib was pulled out of the market by Merck during 2004. In this case also the same scientist Nissen has raised early warning of heart attack and stroke by his research.

These case studies, further testifies the urgent need of a pharmacovigilance program in India for even Generic drugs which are already marketed elsewhere in the world (Biswas and Biswas, 2007).

Pharmacovigilance has not picked up well in India and the subject is in its infancy. India rates below 1% in pharmacovigilance as against the world rate of 5%. This is due to ignorance of the subject and also lack of training. The office of the Drugs Controller General of India has attempted to implement a pharmacovigilance program in India without much success. A regulation is required to implement the system of reporting adverse events of drugs introduced in the Indian market by pharmaceutical companies. The Government has to play an important role in ensuring the availability of safe medicines to public (Ghosh *et al*., 2011).

The mind set of all including the bureaucrats and politicians and healthcare professionals need to be changed. The politicians and bureaucrats need only to support with full powers to the Drugs Controller General of India and the professionals. With the help of all stakeholders, let us pledge to make this happen in India and build a world-class pharmacovigilance system and safe more life from new drug toxicity tragedy.

Pharmacovigilance is a demanding science offering great opportunities for reducing harm to patients and costs to healthcare systems. From small beginnings, with the right knowledge and skills, pharmacovigilance can make an important contribution to the health of the nation

Different classification of anti-diabetic drugs involved in various adverse reactions were assessed during this study. The outcome of the study indicated that biguanides (metformin) has been reported with majority of diarrhoea (abdominal upset) followed by other minor adverse drug reactions. From the sulfonyl urea class we have assessed gliclazide and found

that the major adverse drug reaction was pancreatitis. This could be due to increased stress on the pancreas with limited beta cell to secret insulin for the body requirement. The peptide hormone group insulin was reported with majority with hypoglycaemia and often leads to coma stage. However during our interaction, we did not come across any coma patients. The other major adverse reaction for insulin reported is carcinoma, during our study period we did not come across any carcinoma patients. Our assessment to insulin shows hypoglycaemia as major reported adverse drug reaction. Thiozolidinethione classification drug pioglitazone was assessed for adverse drug reaction and hepatic impairment was reported as main adverse drug reaction. Finally the DPP-4 inhibitor classification Sitagliptin reported with pancreatitis as major adverse drug reaction.

Majority of adverse drug reactions observed from the classification of drugs were between mild to moderate.

7. CONCLUSION

All these adverse drug reports published and available in the public domain has given the inspiration of selecting the current study involving pharmacovigilance in diabetes mellitus treatment. This study also indicated the types of adverse reactions occurred during the diabetes mellitus treatment. In this present study I have selected four different grout of medicines available for diabetes treatment e.g, first line therapy for type-1 diabetes is insulin and first line therapy for type 2 diabetes is metformin, followed by pioglitazone and DPP-4 inhibitor sitagliptin. These drugs have various kind of adverse reactions across age and body weight distribution. From our finding it is evident that female gender is more affected by these adverse reactions than male genders. This could be due to hormonal changes occurs in the female compared to male. Further, the new algorithm followed in this study was well in agreement with the conventional analysis by Naranjo's casualty analysis method. This was further confirmed using kappa test using statistical analysis.

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