A STUDY OF DRUG UTILIZATION PATTERN AND ADVERSE DRUG REACTION PROFILE OF ANTIDIABETIC DRUGS IN PATIENTS ATTENDING A TEACHING HOSPITAL

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirements for the award of the degree of

M.D PHARMACOLOGY

Branch VI

April 2015

CERTIFICATE

This is to certify that this dissertation entitled "**A study of Drug Utilization pattern and adverse drug reaction profile of antidiabetic drugs in patients attending a teaching hospital"** is a bonafide record of the work done by **Dr. Shanthi. M** under my guidance and supervision in the Department of Pharmacology during the period of her postgraduate study for **M.D. Pharmacology [Branch-VI]** from 2012-2015.

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DECLARATION

I Dr. Shanthi. M, hereby submit the dissertation titled "**A study of Drug Utilization pattern and Adverse drug reaction profile of antidiabetic drugs in patients attending a teaching hospital**" done in partial fulfilment for the award of the degree **M.D Pharmacology [Branch-VI]** in Sree Mookambika Institute of Medical Sciences, Kulasekharam. This is an original work done by me under the guidance and supervision of Dr. Rema Menon. N.

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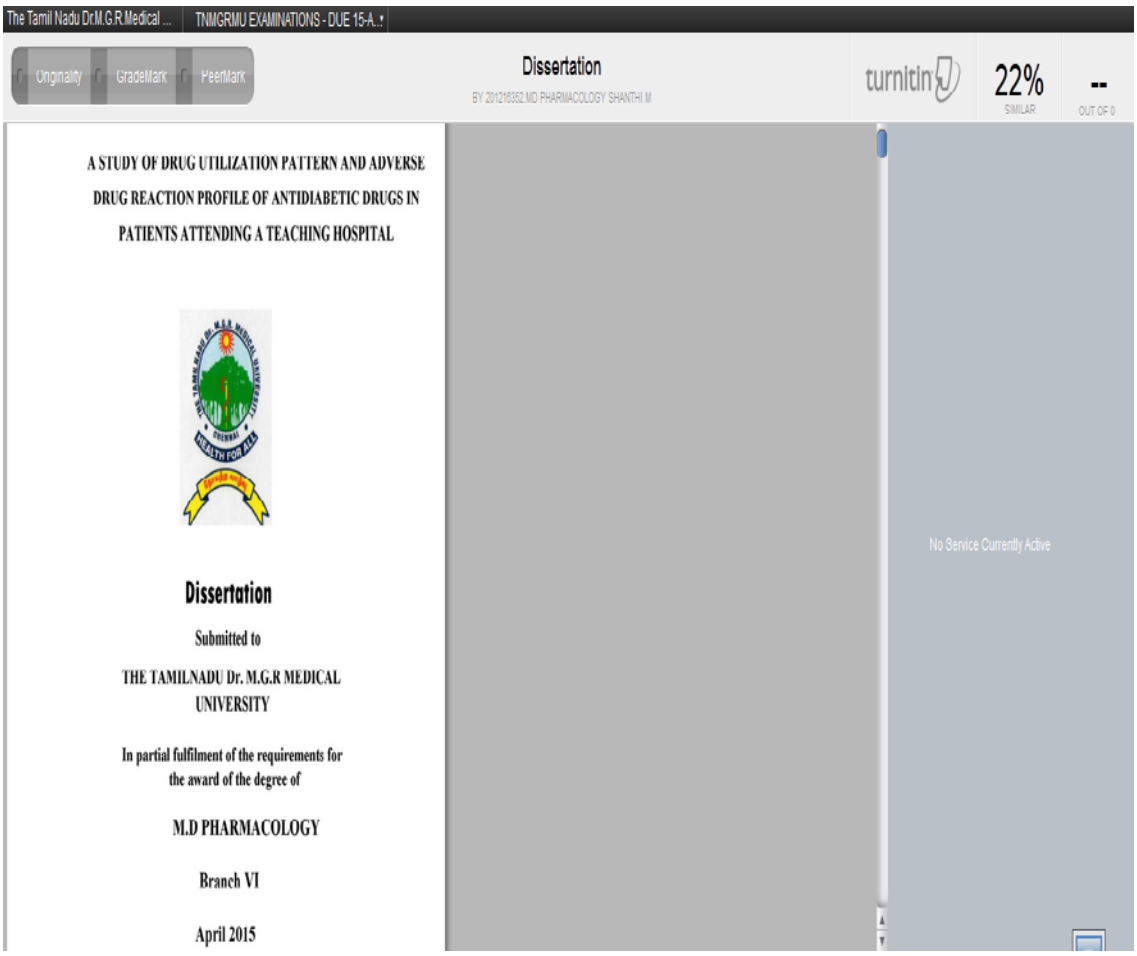
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A STUDY OF DRUG UTILIZATION PATTERN AND ADVERSE DRUG REACTION PROFILE OF ANTIDIABETIC DRUGS IN PATIENTS ATTENDING A TEACHING HOSPITAL

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Aims and objectives:

To study the utilization pattern, rationality, prescription by brand name or generic name, adverse drug reaction profile and pharmacoeconomic analysis of antidiabetic drugs

Materials and Methods:

A cross-sectional study was done for a period of one year (between August 2013 to August 2014) at outpatient department of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari District, Tamil Nadu.

Results:

169 prescriptions were evaluated during the study period. DM was predominant among the female population in this region. Demographic details of the patient included in the study were mean weight 67.56 kg, mean height 155 cm and average body mass index 27.82 kg/m^2. All the patients were

diagnosed as type 2 DM and majority being known case of DM. Systemic hypertension was the frequently encountered co-morbid conditions associated with DM. Metformin was the drug chosen for managing DM as monotherapy. 73% of the patients were on combination of antidiabetic drugs. Glimepiride with metformin was the two drug combination therapy frequently prescribed during the study period. Adverse drug reactions reported during the study were hypoglycemia, gastrointestinal discomfort, edema, rashes and myalgia. Majority of ADRs assessed were probable by WHO scale and possible by Naranjo scale. Modified Schumock and Thornton scale assessed many ADRs to be not preventable. As per the modified Hartwig and Siegel scale none of the ADRs were severe. Pharmacoeconomic analysis identified that drugs prescribed by brand name were costlier compared to generic equivalent. Various antidiabetic drugs were prescribed during the study period in which least expensive was glibenclamide and most expensive was sitagliptin.

Conclusion:

Utilization of antidiabetic therapy in this region has shown a changing trend compared to the previous studies. There is a gradual increase in the prescription of metformin and dramatic increase in the use of newer drugs like pioglitazone, voglibose and sitagliptin. Adverse effect more noted in our study was hypoglycemia. Glibenclamide was the least expensive while sitagliptin was the most expensive in this study.

1. Introduction:

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to absolute or relative deficiency of insulin.[1] This non communicable disease is an emerging epidemic and India topped the world in 2007 with 31.7 million population affected with DM.[2] Prevalence of DM is progressing rapidly worldwide. Currently 285 million are affected by diabetes globally.[3] In India, 62 million are diagnosed to be diabetic and is estimated to reach 79.4 million by 2030.[1] Study on global prevalence of DM predicted that the annual growth will be 2.2% which is double the growth of adult population.[4] Prevalence of DM in Tamil Nadu was found to be 10.4% in a study done by *Anjana et al*.[5]

DM has a major impact on life style of the affected population. Food plays an important role in the development of this metabolic disorder along with genetic and environmental factors. Insulin is a polypeptide hormone secreted by β islets of Langerhans in the pancreas. It is an anabolic hormone which will increase the storage of glucose and help in the conversion of glucose to fat and proteins. Hyperglycemia, the cardinal feature of DM develops due to reduced insulin secretion or reduced glucose utilization.[1,6,7]

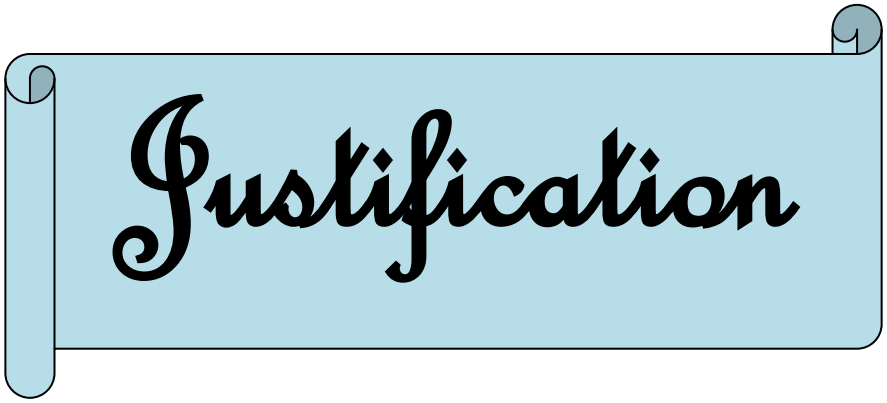
Manifestations of hyperglycemia are polyuria, polydypsia, polyphagia and weight loss. Acute life threatening consequence of uncontrolled DM is diabetic ketoacidosis and hyperglycemic hyperosmolar state. Multiple organs undergo secondary patho physiological changes due to this altered metabolism. Majority of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness are complications due to DM. [1,6,7]

Management of DM require both non pharmacological and pharmacological interventions. Parenteral Insulin preparation and oral hypoglycemic medication are the currently available pharmacotherapy of DM. Management of hyperglycemia with appropriate drugs can prevent both short term and long term complications of DM.[1,6,7]

Drug utilization identifies the use of drugs in a society considering medical, social and economic consequences. Drug utilization study (DUS) can predict the rational use of drug in a population. Drug prescribed is considered rational if the patients receive medication appropriate to their clinical needs in doses that meet their own individual requirements for an adequate period of time and at the lowest cost to them and their community.[8]

Adverse drug reaction (ADR) accounts for morbidity and repeated hospital admission. Identification of adverse drug reactions is lacking in studies conducted in India and ADR monitoring and reporting is in the stage of infancy in India. In a study done by *Mandavi et al*.[9] it was pointed out that 3.4-7% of hospitalization was due to ADR.

DM requires lifelong therapy and one of the important factor deciding compliance of patient is the cost of therapy. There is a wide variation in prescription of antidiabetic drugs with increasing concern about ADR and cost of therapy. Understanding the importance of DUS is rapidly growing worldwide. Hence rationality of antidiabetic therapy can be justified by treating the ailment with appropriate drug that can ensure immense therapeutic benefit in patients with least ADR and a minimum cost of therapy.[9]


Justification

2. Justification:

Response to antidiabetic agents varies in different population. Unawareness towards regional distribution of DM is a major drawback in India.[10] Drug utilization research (DUR) establishes the current trend in the use of anti diabetic drugs and adverse drug reactions including the new drug and to identify irrational prescription. Irrational prescription can affect the adherence to drugs thereby not reaching therapeutic goal ultimately rising the economic burden.

Till date no study on drug utilization pattern and ADR profile of antidiabetic drugs is conducted in this institution. Hence it has been proposed to conduct the study to evaluate the drug utilization pattern and ADR profile of antidiabetic drugs in the Medicine out-patient department (OPD) of this institution.

Aims and Objectives

3. Aims and Objectives:

To assess the following in the OPD of Medicine, Sree Mookambika Institute of Medical Sciences Kulasekharam (Kanyakumari district, Tamil Nadu):

1. The pattern of antidiabetic drugs prescribed
2. Rationality of using antidiabetic drugs as monotherapy and combination therapy
3. Prescription writing pattern by brand name and generic name
4. The pharmacoeconomics of antidiabetic drugs prescribed for one month
5. To study adverse drug reaction profile of antidiabetic drugs prescribed

Review of Literature

4. Review of literature:

4.1. Diabetes Mellitus:

4.1.1. Introduction:

DM is a chronic endocrine disorder characterized by high blood glucose concentration caused by insulin deficiency combined with insulin resistance.[1] There is a growing prevalence of DM worldwide and a rise in the number of the affected people from 285 million to 438 million is expected by the year 2030 and may reach an epidemic proportion.[10] Major proportion of increase is seen in developing country like India is facing a rapid rise in non communicable disease like DM along with communicable disease. The focus is still on infectious disease control and there is a gross negligence towards non-communicable disease.[11]

This metabolic disorder predominantly affects the economically productive age group.[12] If not managed rationally can lead to microvascular and macrovascular complication. Uncontrolled DM can result in a significant health burden on both family and the public.[12]

4.1.2. History[13,14]

Table No1: Historical landmark and the scientist contributed to DM

Year	Scientist	Historical landmark
1910	Sir Edward Albert Sharpey-Schafer's	Insulin from latin word Insula - Island
1921	Frederick Banting and Charles best	Extract insulin from dog pancreas
1923	Banting and Macleod	Nobel prize in Physiology or Medicine

Table No 2: Discovery of antidiabetics

Year	Antidiabetic discovered
1936	Protamine insulin
1955	Sulphonylurea
1990	Incretin hormone GLP-1
1995	Metformin
1996	Acarbose
1997	Thiazolidinediones
1998	Repaglinide
2005	Incretin mimetic - Exenatide
2005	Pramlintide
2006	DPP-4 inhibitors
2013	SGLT-2 inhibitors

GLP-1: Glucagon like peptide 1

DPP-4 inhibitors: Dipeptidyl peptidase 4 inhibitors

SGLT-2 inhibitors: Sodium glucose co-transport 2 inhibitors

4.1.3. Definition:

"The term Diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of

carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both."[15]

4.1.4. Epidemiology:[10]

Indian population currently gaining the status of potential epidemic in India since individuals diagnosed with DM is more than 62 million. India topped the world with highest number of people (31.7 million) with DM in 2000.[1] Percentage of individuals in pre-diabetic state is 62.4 million. It is predicted that by 2030 patients in pre-diabetic state will be 101 million in India.[16] Prevalence has been found to be equally affecting both the rural and urban population.[5]

4.1.5. Classification of DM[17,18]

DM is classified based on the pathological process that leads to hyperglycemia. The major common types of DM are :

Table No 3: Major types of Diabetes mellitus

S. No	Type	Pathology Inducing hyperglycemia
1.	Type 1 DM	β cell depletion: ❖ Immune mediated or ❖ Idiopathic
2.	Type 2 DM	❖ Majority of cases due to insulin resistance ❖ Insulin secretory defect predominates ❖ Relative insulin deficiency
3.	Gestational	Pregnancy induced

Table No 4: Genetic and immune mediated types of DM

i. Genetic defects	**Type of DM**
a. β cell function	
Hepatocyte nuclear transcription factor 4 α (HNF 4 α)	Maturity Onset Diabetes of Young 1 {MODY 1}
Glucokinase	MODY 2
HNF 1 α	MODY 3
Insulin promoter factor-1 (IPF-1)	MODY 4
HNF 1 β	MODY 5
Neuro DI	MODY 6
Mutation leading to β cell dysfunction	Mitochondrial DNA Subunits of ATP sensitive potassium channel Proinsulin or Insulin
b. **Insulin action**	▪ Type A insulin resistance ▪ Leprechaunism ▪ Rabson-Mendenhall syndrome ▪ Lipodystrophy syndromes
ii. **Others**	Wolfram's syndrome Down's syndrome Klinefelter's syndrome Turner's syndrome Friedreich's ataxia Huntington's chorea Laurence Moon-Biedl syndrome Myotonic dystrophy Porphyria Prader-Willi syndrome

Drug or chemical induced DM:

Glucocorticoids, β adrenergic agonists, thiazides, hydantoins, α interferon, protease inhibitors, antipsychotics, nicotinic acid induces DM.

Development of DM due to disease and infection of pancreas are:

Table No 5: Pancreatic disorders leading to development of DM

Defect	Pathology
i. **Exocrine pancreas**	▪ Pancreatitis ▪ Pancreatectomy ▪ Neoplasia ▪ Cystic fibrosis ▪ Hemochromatosis ▪ Fibrocalculous pancreatopathy ▪ Mutations in carboxyl ester lipase
ii. **Endocrine disorder**	▪ Acromegaly ▪ Cushing's syndrome ▪ Glucagonoma ▪ Pheochromocytoma ▪ Hyperthyroidism ▪ Somatostatinoma ▪ Aldosteronoma
iii. **Infection**	Congenital rubella, Cytomegalovirus, Coxsackievirus

4.1.6. Factors contributing to the development of Diabetes mellitus:[2,12]

Type 1 DM:

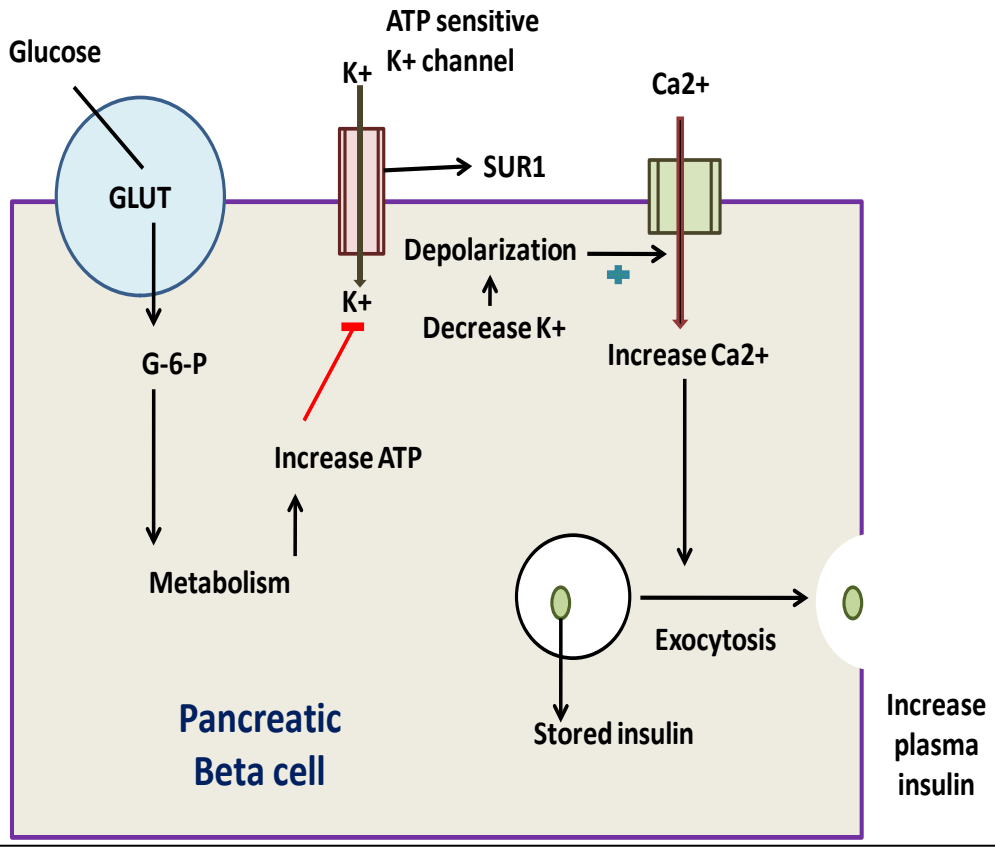
Patients susceptible to autoimmune destruction of β cell is triggered by:

- Intra-uterine infection and low birth-weight
- Viral infections like mumps, rubella, coxsackie B and cytomegalovirus
- Chemical toxins
- Dietary components
- Environmental factors
- Congenital rubella

Type 2 DM:

Factors pre-disposing to the development of type 2 DM can be either modifiable or non-modifiable.

Figure 1: Regulation of insulin secretion from pancreatic β cell



Modified from Powers CA, D'Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In. Laurence LB, John SL, Keith LP editors. Goodman & Gilman's Pharmacological Basis of Therapeutics 12thed. New Delhi. McGraw-Hill. 2011; p.1238-73.

.i. Non-modifiable risk factors[11]

- Age (more than 45 years)
- Family history of diabetes
- Diabetes during a previous pregnancy

ii. Modifiable risk factors[11]

- Physical inactivity
- Diets rich in saturated fats and simple carbohydrates
- Impaired glucose tolerance
- Cigarette smoking
- Increased consumption of alcohol
- Obesity – risk in developing DM is 55%

4.1.7. Pathogenesis:[2,19,20]

Type 1 DM

5 to 10% of type 1 DM develops due to autoimmune destruction of β cells of the pancreas. Manifestations of DM develop only after 70 to 80% of β cells are destroyed. Normal β cell mass is seen in individuals with genetic susceptibility at birth. Infection or environmental stimuli are the triggering factor for the autoimmune process.

i. Genetic factors

Major risk (40 to 50%) associated with DM is Human leukocyte antigen (HLA) locus on chromosome 6p21. It reflects the ability of specific HLA molecules to present self antigens. Non HLA genes also increase susceptibility to type 1 DM. Polymorphism of genes inhibiting T cell response can result in excessive T cell activation.

ii. Environmental factors

Triggering factors involved in islet cell destruction are viral infection like mumps, rubella, coxsackie B and cytomegalovirus. Viral infections induce autoimmunity by:

- Inducing islet injury and inflammation releasing sequestrated β cell antigens and activate auto reactive T cells
- Producing proteins that mimic β cell antigens and immune response to the viral protein cross reacts with self tissue

Characteristic features of type 1 DM are:

- Circulating insulin levels are low or very low
- Patients are more prone to ketosis

Type 2 DM:

Lifetime risk of developing type 2 DM increases if both parents are affected. Variant of transcription factor 7 on chromosome 10q is associated with type 2 DM and impaired glucose tolerance. Genes involved in developing DM are not linked to immune regulation.

Decreased response of peripheral tissue to insulin and β cell dysfunction is the metabolic defects that characterise this type of DM.

Characteristic feature seen here are:

- No loss or moderate reduction in β cell mass
- Insulin in circulation is low
- No anti β cell antibody is demonstrated
- High degree of genetic predisposition

- Late onset

4.1.8 Mechanism of DM:[2, 19]

Type 1

In this type of disorder there is β cell destruction in pancreatic islets and autoimmune process starts years before the disease manifest. The major targets of immune attack includes insulin, β cell enzyme glutamic acid decarboxylase and islet cell autoantigen. In majority of cases there are autoimmune antibodies (Type 1A) that destroy β cells detectable in blood. Type 1 B is an idiopathic condition with no detectable β cell antibody.

Type 2

It is a multifactorial complex disease and majority (90%) of cases are due to type 2 DM.

DM manifest due to abnormality in gluco-receptor of β cell so that they respond at higher glucose concentration. There may be reduced sensitivity of peripheral tissues to insulin, reduction in number of insulin receptors and down regulation of insulin receptors. Excess of hyperglycemic hormones or obesity can lead to relative insulin deficiency.

4.1.9. Clinical features:[2, 21]

- **Polyuria**: Increased urinary output
- **Polydypsia**: Increased thirst
- **Polyphagia**: Increase in appetite
- Unexplained weight loss
- Numbness in the feet, legs or hands
- Healing of wound delayed

- Mood swings
- Fatigue
- Headache
- Fainting

4.1.10. Diagnosis:[18]

- Glycosylated Haemoglobin [HbA1C] more than 6.5%
- Fasting plasma glucose level > 126 mg/dl
- Oral glucose tolerance test: Following a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water and 2 hour plasma glucose shown above 200 mg/dl (or)
- Presence of classical symptoms of hyperglycemia like polyuria, polydypsia, weight loss with polyphagia and a random plasma glucose more than 200 mg/dl

4.1.11. Pathological consequences:[3,7,19,22,23]

DM can cause acute life threatening metabolic derangements like diabetic ketoacidosis and hyperglycemia hyperosmolar coma. Chronic complication can be:

i. Macrovascular: Increase risk of myocardial infarction, stroke and lower extremity gangrene

ii. Microvascular: Characteristic of DM patient includes retinopathy, nephropathy and neuropathy

4.1.12. Treatment:[2]

Non-pharmacological:

1) Balance diet rich in fibre and control of total calories and free carbohydrates intake
2) Exercise
3) Smoking cessation and reduction of alcohol intake

Pharmacological:[5]

1) Insulin
2) Insulin secretagogue
3) Glucagon-like Polypeptide-1 (GLP-1) Receptor Agonists
4) DiPeptidyl Peptidase-4 (DPP-4) Inhibitors
5) Insulin sensitizers
6) α-Glucosidase Inhibitors

Surgical:[24]

Bariatric surgery involving resection of small intestine is indicated in type 2 DM with body mass index (BMI) more than 35 kg/m2. Surgery can lead to normalization of glycemia in 40 to 95% of type 2 DM patients.

4.2. Antidiabetic drugs:[5,6,7,18,25-33]

Pharmacotherapy is mandatory to maintain an optimal glycemic control in the management of DM. DM can be treated either with oral hypoglycemic agents or parenteral insulin therapy. Different classes of antidiabetic drugs act at different parts of this glucose-insulin pathway which includes drugs that increase the amount of insulin secreted by the pancreas, increase the sensitivity of target organs to insulin and decrease the rate at which glucose is

absorbed by the gastrointestinal tract. The number of available oral hypoglycemic agents shows a transient rise in the last decade. Decision making by physicians has become complex with more therapeutic options. Treatment of diabetes requires a progressive pharmacological approach. Irrational management of DM and its adverse effect can have a major public health impact.[3]

4.2.1. Classification

Table No 6: Classification of antidiabetic drugs

Sl. No	Class	Drugs
1.	Insulin	Rapid-acting: Lispro, Aspart, Glulisine Short acting: Regular Intermediate acting: NPH (Neutral Protamine Hagedorn or Isophane) Long acting: Detemir, Glargine
2,	Sulphonylurea	First generation: Chlorpropamide Tolbutamide Second generation: Glibenclamide (Glyburide) Glimepiride Glipizide Gliquidone Gliclazide
3.	Meglitinides	Repaglinide Nateglinide
4.	Glucagon like peptide 1 agonist	Exenatide

		Liraglutide
5.	Dipeptidyl peptidase-4 inhibitor	Sitagliptin Vildagliptin Saxagliptin Alogliptin Linagliptin
6.	Biguanides	Metformin Phenformin Buformin
7.	Thiazolidinediones	Pioglitazone
8.	α- glucosidase inhibitor	Acarbose Miglitol Voglibose
9.	Amylin agonist	Pramlintide
10.	Sodium-glucose co-transport-2 (SGLT-2) inhibitor	Dapagliflozin

4.2.2. Individual classes of Drugs:

4.2.2.1. Insulin:

Insulin is the choice of drug for all forms of DM and bioavailable only when administered parenterally. Clinically used insulin is expressed in international units. One unit of insulin reduce blood glucose concentration in fasting rabbit to 45 mg/dl. Insulin absorption and pharmacokinetics are modified by two approaches:

- Formulation slowing absorption following subcutaneous injection
- Human insulin protein structure and aminoacid sequence alteration

1. Rapid-acting:

Very fast onset and duration of action is short (4 to 5 hours). It has comparatively a lowest variability of absorption (5%).

i. **Insulin Lispro:** First monomeric insulin analog produced by Recombinant technology. Structure of insulin altered by reversal of amino acid in the carboxy terminal of B-chain (B28: Proline, B29: Lysine). Onset of action seen in 5 to 15 min and peak activity at 1 hr.
ii. **Insulin Aspart:** Modification of Insulin by substitution with aspartic acid at B28 (proline) there by inhibiting Insulin aggregation.
iii. **Insulin Glulisine:** Lysine substituted at B3 and glutamic acid at B29. These modifications alter the downstream of events in insulin receptor substrate 2 (IRS-2) pathway.

2. Short-acting:

Soluble crystalline zinc Insulin:

Effect of insulin appears within 30 minutes and peak effect occurs within 2 to 3 hour. Regular insulin molecules aggregate to form dimers which stabilize around zinc ions to form hexamers. Action is based on hexameric nature of regular Insulin. Disadvantage of using regular insulin are delayed absorption, dose dependent duration of action of insulin and variability of absorption (25%). It is the only insulin that can be administered intravenously because on dilution hexamers immediately dissociate into monomers.

3. Intermediate-acting:

Absorption of NPH is delayed by combining appropriate amount of insulin and protamine so that it is in a complex state. After subcutaneous

injection proteolytic tissue enzymes degrade protamine to permit absorption of insulin. Onset of action in 2 to 5 hrs and duration of action is 4 to 12 hrs.

4. Long-acting:

Insulin Glargine:

This is the soluble long acting preparation and has a slow onset of action (1 to 1.5 hrs) and maximum effect seen after 4 to 6 hrs. Two arginine molecules attached to B–chain carboxyl terminal and glycine at A21 position. This altered analog is soluble in acidic solution but precipitates at body neutral pH. Insulin from crystalline depot slowly dissociates to maintain a low continuous level of circulating insulin. It should not be mixed with other insulin (to maintain solubility, the formulation is maintained at acidic pH).

Insulin Detemir:

This is recently developed long acting insulin. Onset of action is between 1 to 2 hrs which is dose dependent with duration of action for more than 12 hrs. Terminal threonine is dropped from B30 and myristic acid is attached to terminal B29. This modification increase both self aggregation and reversible albumin binding thereby prolonging the availability of injected insulin. Development of hypoglycaemia is minimal compared to NPH.

Mechanism of action:

Insulin receptor is a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunit linked by disulfide bonds. Insulin binding site is present in α subunit while tyrosine protein kinase activity is in β subunit. Binding of insulin to α subunit, internalise the receptor and enhance tyrosine kinase activity. Autophosphorylation of tyrosine residues of

β subunit increase the tyrosine phosphorylation of Insulin receptor substrate proteins. Activation of phospholipase C generates certain second messengers like phosphotidyl inositol glycan and diacylglycerol.

- Both phosphorylation and second messengers are involved in the rapid metabolic action of Insulin.
- Stimulates transport of glucose across cell membrane by ATP dependent translocation of glucose transporter 4 (GLUT4) and GLUT1 to plasma membrane.
- Promote expression of genes directing synthesis of GLUT.

Fate of internalized receptor-insulin complex:

- Degraded intracellularly
- Return back to surface

Indication:

1. Type 1 and 2 DM
2. Diabetic ketoacidosis: Life threatening medical emergency caused by inadequate insulin replacement. Commonly seen in-
    - Type 1 DM – Newly diagnosed or interrupted insulin replacement
    - Type 2 DM – Concurrent stressful condition (sepsis, pancreatitis, high dose steroid therapy)

    Clinical presentation:

    Nausea, vomiting, abdominal pain, deep slow breathing (Kussmaul), changes in mental status, elevated blood and urinary ketones and glucose, low arterial pH and bicarbonate.

3. Hyperosmolar hyperglycemic syndrome: Type 2 DM patient with hyperglycemia and dehydration.

   Predisposing factor:

   - ❖ Inadequate oral hydration
   - ❖ Elderly
   - ❖ Drugs – Phenytoin, steroids, diuretics, β blockers
   - ❖ Peritonealdialysis and haemodialysis

   Clinical presentation:

   Declining mental status, seizure, plasma glucose > 600mg/dl

Adverse drug reaction:

1. Hypoglycemia: Most common complication due to-

   - ❖ Inadequate carbohydrate consumption
   - ❖ Unusual physical exertion
   - ❖ Too large dose of insulin

   Clinical presentation:

   - ❖ Intact hypoglycemic awareness

     Sympathetic (tachycardia, palpitation, sweating)

     Parasympathetic (nausea, hunger)

   - ❖ Hypoglycemic unawareness

     Important feature found in patients exposed to frequent episodes of hypoglycemia. These patients lack early warning sign of reduced plasma glucose concentration. By preventing repeated exposure to hypoglycemia, awareness can be restored.

2. Insulin allergy:

   Local or systemic urticaria due to histamine release from tissue mast cell sensitised by antiinsulin immunoglobulin E (IgE) antibodies.

3. Immune insulin resistance:

   Patients on insulin always have a circulating immunoglobulin G (IgG) antiinsulin antibody at a low concentration which will neutralize the action of insulin to a negligible extent. Sometimes insulin resistance may develop due to the auto antibodies.

4. Lipodystrophy:

   Animal insulin preparation may produce atrophy of subcutaneous fatty tissue at the site of injection

5. Increased cancer risk:

   Due to insulin resistance and hyperinsulinemia

Contraindications:

- During episodes of hypoglycemia
- Hypersensitive to insulin

4.2.2.2. Sulphonylurea:

Sulphonylurea were the first widely used oral antidiabetic treatment. Sulphonylurea are approved for use as monotherapy and in combination with insulin and other oral hypoglycemic agents (OHA) except with rapidly acting secretagogues.

Route of administration: Oral and advice to take immediately before meals.

Mechanism of action:

Sulphonylurea binds to β cell sulphonylurea receptor 1 (SUR-1) [Part of transmembrane complex with adenosine 5'-triphosphate sensitive potassium adenosine triphosphate channel (K_{ATP} channel)]. Binding of sulphonylurea to the SUR-1 receptor closes the K_{ATP} channel. Depolarisation open voltage dependent calcium channel and activation of calcium-dependent protein release insulin granules by exocytosis. Later insulin action declines but there are sensitization of the target tissue to the action of insulin. This is due to increase in the number of insulin receptor and there is reduction in HbA1C level by 1 to 2%.[20]

Adverse drug reaction:

i. Hypoglycemia

   20% report one episode annually. Insulin release is initiated when glucose concentration are below the normal threshold for glucose-stimulated insulin release. Elderly diabetic patients who were treated with sulphonylurea have a 36% increased risk of hypoglycemia compared to younger patients.

ii. Transient cutaneous reaction

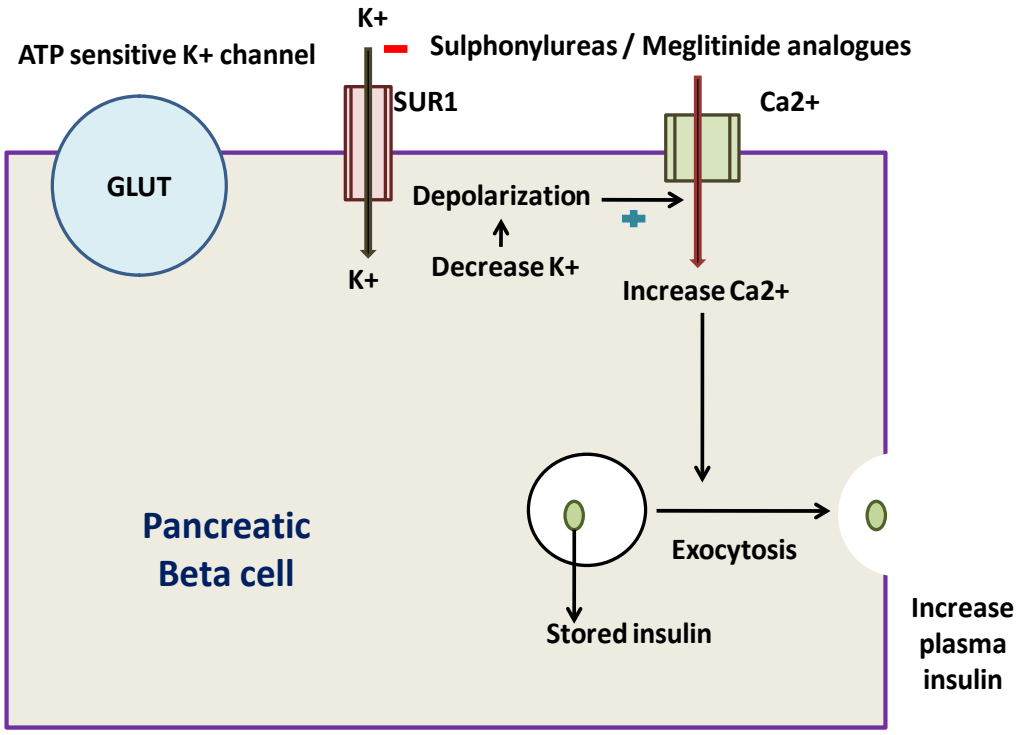
iii. Fever, jaundice, blood dyscrasia

iv. Chlorpropamide with alcohol cause facial flushing

v. Chlorpropamide increase renal sensitivity to anti diuretic hormone causing water retention with hyponatremia

vi. Weight gain of 1 to 4 kg and stabilize after 6 months. It is due to anabolic effect of increased plasma insulin concentration.

Figure 2: Mechanism of action of Sulphonylurea and Meglitinide



Modified from Powers CA, D'Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In. Laurence LB, John SL, Keith LP editors. Goodman & Gilman's Pharmacological Basis of Therapeutics 12thed. New Delhi. McGraw-Hill. 2011; p.1238-73.

Drug Interactions

Drugs increasing sulphonylurea action are phenylbutazone, salicylates, sulphonamides, sulfinpyrazone which displace sulphonylurea from the protein binding sites. Cimetidine, ketoconazole, sulphonamides, warfarin, chloramphenicol and acute alcohol intake can Inhibit the metabolism of sulphonylureas. Salicylates, propranolol, sympatholytic antihypertensive, lithium, theophylline and alcohol can prolong the pharmacodynamic action of sulphonylureas.

Drugs decreasing sulphonylurea action are phenobarbitone, phenytoin, rifampicin, chronic alcoholism which may induce the metabolism of sulphonylurea. Corticosteoids, thiazide, furosemide and oral contraceptives will suppress the insulin release due to sulphonylurea.

Contraindication:

i. History of hypersensitivity
ii. Diabetic ketoacidosis
iii. Hepatic disease
iv. Renal disease
v. Pregnant and lactating ladies

4.2.2.3. Meglitinide / D-phenylalanine analogues:

Meglitinides are novel antidiabetic medicine and can be given in combination with other antidiabetic drugs when hyperglycemia is not controlled.

Route of Administration: Oral, half an hour before each meal

Mechanism of action:

Meglitinides are highly tissue selective and have a low affinity for heart and skeletal muscle. It binds with the ATP dependent potassium channel in the β cell of pancreas but the site is distinct from that involved in sulphonylurea binding. Binding of meglitinide to the potassium channel will block the potassium channel and increases the calcium influx and induces insulin secretion. They are effective in lowering glycated haemoglobin level by 0.6 to 1%.

Adverse drug reaction:

i. Hypoglycemia: 16% of patients (Because of short lasting action, risk of hypoglycemia is less)
ii. Headache, dyspepsia, arthralgia, weight gain
iii. Dizziness, nausea, flu like symptoms, joint pain

Contraindication:

i. Hepatic dysfunction
ii. Diabetic ketoacidosis
iii. Type 1 DM
iv. Known hypersensitivity reaction

4.2.2.4. Incretin based therapy:

Insulin and glucagon levels are influenced by incretin hormones called

- GLP-1 secreted by the intestinal glucose responsive neuroendocrine (L) cells of the intestinal mucosa after a meal
- Glucose dependent insulinotropic polypeptide (GIP) secreted by intestinal K cells located in the jejunum and throughout the gut

Both exert an insulinotropic effect (glucose dependent secretion of insulin). GLP-1:

- Stimulates insulin secretion and inhibits glucagon secretion under hyperglycemic condition
- Slows gastric emptying and acts as a mediator of satiety in the central nervous system

Incretin effect is the phenomenon by which greater insulin secretion occurs after oral glucose intake than after the infusion of comparable amounts of intravenous glucose.

Patients with type 2 diabetes lack the insulinotropic response to GIP. GLP-1 levels may be reduced in this patient population resulting in a much more physiological regulation of α and β cell function and minimize the risk for hypoglycemia.

GLP-1 and GIP are rapidly degraded by the proteolytic enzyme DPP-4 and thus are available only for a very short time.

4.2.2.4.A. Incretin mimetic: Exenatide, Liraglutide

Route of administration: Subcutaneous injection, administered in the abdomen, thigh or upper arm

Mechanism of action

Incretin mimetics are synthetic peptide. It is DPP-4 resistant analogue which exhibits same biological effect as GLP-1. It has a longer half life. Results in a significant reduction in glycosylated haemoglobin level and reduce body weight.

Adverse drug reaction

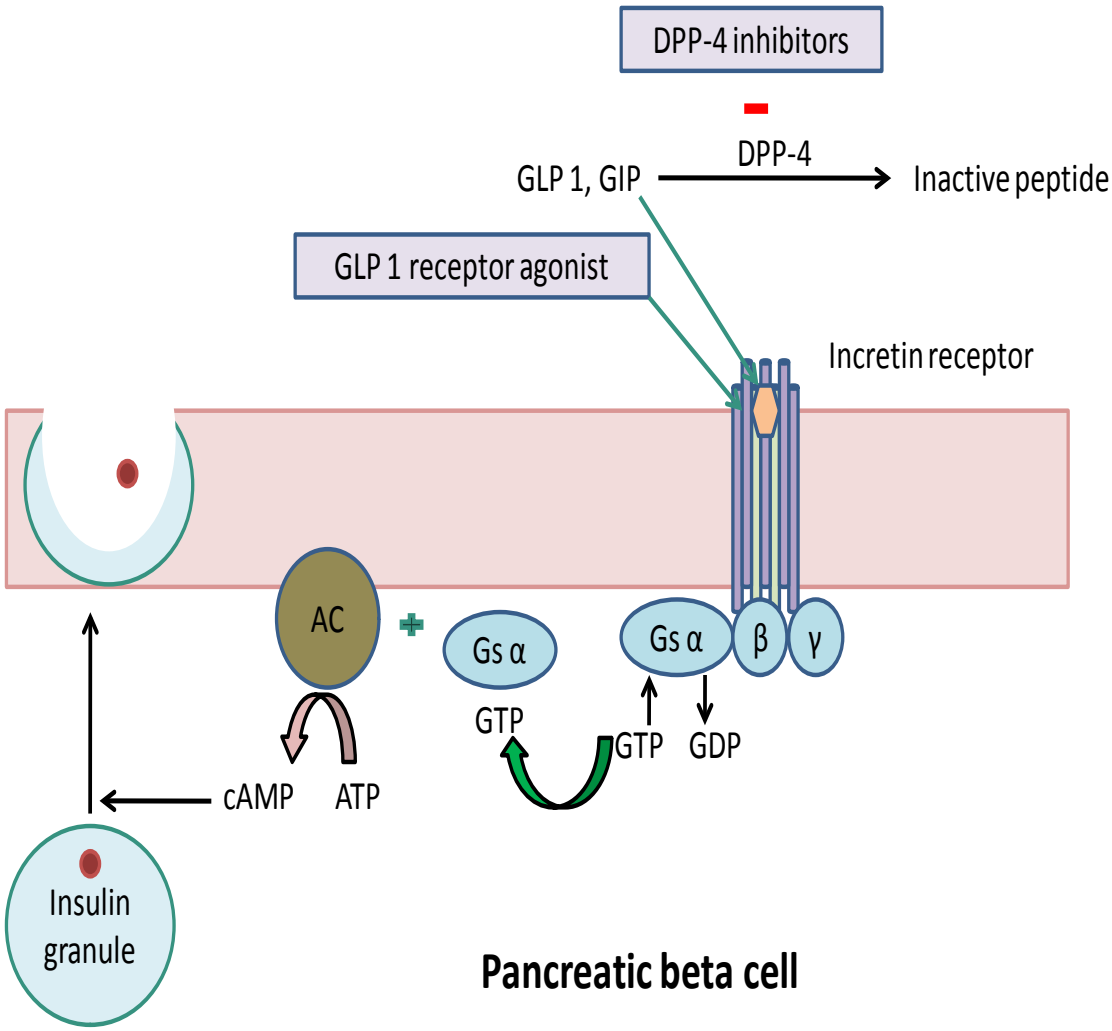
i. Nausea, vomiting in 50% recipients
ii. Diarrhea
iii. Acute pancreatitis
iv. Hemorrhagic or necrotizing pancreatitis

Contraindication:

Renal impairement

4.2.2.4.B. Dipeptidyl peptidase-4 inhibitors:

Figure 3: Mechanism of action of DPP-4 inhibitors



Modified from Tripathi KD. Essentials of medical pharmacology. 7th ed. New Delhi: Jaypee brothers medical publishers; 2013. p.512-38.

Route of administration: Oral

Mechanism of action:

DPP-4 inhibitors prevent the degradation of GLP-1 and GIP thus increasing endogenous incretin level

Adverse drug reaction:

- Nausea
- Loose stools
- Rashes
- Allergic reaction
- Upper Respiratory tract infections
- Dizziness
- Influenza
- Headache
- Hepatotoxicity reported with vildagliptin
- Nasopharyngitis and cough due to prevention of substance P degradation

Contraindication:

History of hypersensitivity reaction

4.2.2.5. Biguanides:

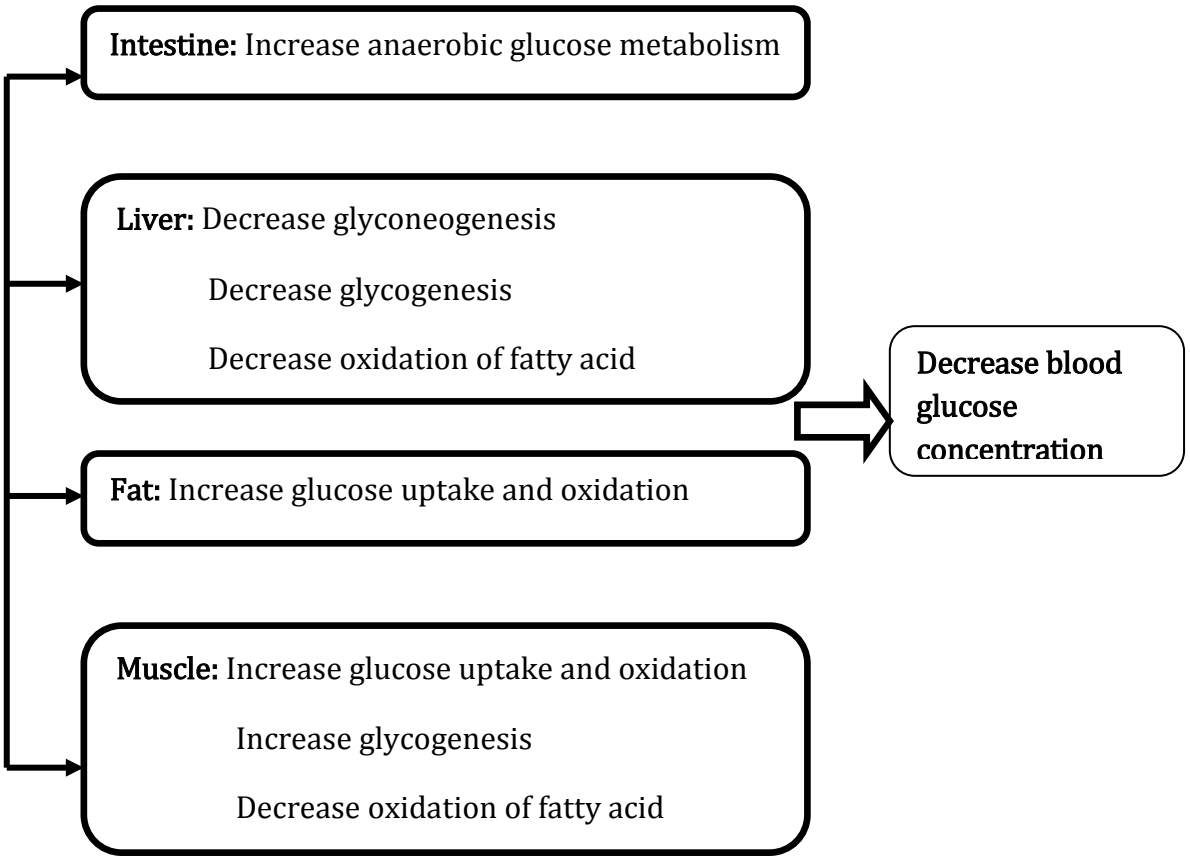
Biguanides are insulin sensitizers which reduce hepatic glucose output and increase in utilization of glucose by the peripheral tissues. A very salient feature of this class of drug is associated with weight loss and lower incidence of hypoglycaemia as monotherapy.

Route of Administration: Oral

Mechanism of action:

Presence of insulin is essential for their action. Mechanism by which metformin exerts its antihyperglycemic effect are not entirely clear. Adenosine 5' monophosphate activated protein kinase (AMPK) is a intracellular target of metformin.

Figure 4: Effect of Metformin



They reduce the HbA1C by 1 to 2%.

Non Diabetic Indication:

Anovulatory polycystic ovary syndrome (PCOS) – improvement of insulin sensitivity cause ovulation to resume

Adverse drug reaction:

i. Abdominal discomfort and diarrhea

ii. Nausea, metallic taste, tiredness

Lactic acidosis – Increase in blood lactate because it is poorly concentrated in hepatic cells. Precipitated by alcohol ingestion. 0.03 cases per 1000 patient-years or 1 case per 33,000 patient-years. Phenformin and buformin were withdrawn in 1980s due to lactic acidosis which can be fatal

iii. Vitamin B12 deficiency due to interference with its absorption

Drug interaction:

Cimetidine and furosemide compete with metformin excretion and enhance its toxicity

Contraindication:

- Impaired renal function
- Conditions predisposing to hypoxia or reduced perfusion
- Liver disease
- Alcohol abuse
- History of metabolic acidosis

4.2.2.6. Thiazolidinediones:

Glitazones were introduced in the year 1997. The most prominent effect of thiazolidinediones is to increase insulin stimulated glucose uptake by skeletal muscle cells.

Route of Administration: Oral

Mechanism of action:

Peroxisome prolferator activated receptors (PPARs) are transducer proteins belonging to nuclear receptor super family. PPAR gamma is a transcription factor activated by thiazolidinediones. On transactivation, which is DNA dependent, PPAR gamma forms a heterodimer with the Retinoid X receptor (RXR). Specific DNA response elements called PPAR Response Elements (PPRE) are recognized in the promoter region of the target genes. Peroxisome proliferator activated receptor gamma (PPAR gamma) is expressed at highest level in adipose tissue and less in muscle and liver. They promote differentiation of pre-adipocytes with lipogenesis that enhance the local effect of insulin occurs. Increased glucose uptake via GLUT-4 in skeletal muscle and reduce the production and activity of adipocyte derived cytokine tumour necrosis factor α (TNF α) implicated in the development of impaired insulin action in the muscle.

Adverse drug reactions:

- Fluid retention
- Weight gain
- Myalgia
- Mild anemia

- Increased risk of heart failure
- Hepatitis and liver damage
- Troglitazone were withdrawn in 2000 due to risk of hepatitis and liver damage
- Rosiglitazone use for 12 months is associated with a significantly increased risk for myocardial infarction and heart failure

Drug Interaction:

- Failure of oral contraception
- Ketoconazole inhibits metabolism – Increase the concentration of pioglitazone
- Rifampicin induces metabolism – Decrease the concentration of pioglitazone

This is because pioglitazone is metabolised by both CYP2C8 and CYP3A4

Contraindication:

- Diabetic ketoacidosis
- Active liver disease
- Heart failure
- Insulin treatment: Greater fluid retention, weight gain and precipitation of congestive heart failure
- Pregnancy and breast feeding

4.2.2.7. α - Glucosidase inhibitors:

α - glucosidase inhibitor competitively inhibits enzymes in the small intestine that are responsible for breakdown of oligosaccharide and disaccharide into monosaccharide suitable for absorption. They do not target

specific pathophysiologic aspects of diabetes. There is a surprising improvement in the post prandial plasma glucose level. They are most useful in combination with other oral hypoglycemic agents.

Route of administration: Oral and taken with meals

Mechanism of action:

α glucosidase enzyme is present in the brush border of enterocytes lining the intestinal villi completing the carbohydrate digestion. A glucosidase inhibitors competitively inhibit the activity of this enzyme preventing the cleaving of normal disaccharide into monosaccharide prior to absorption. The average HbA1C lowering effect is about 0.5 to 1% which is comparatively lesser than other class of OHA. They alter the release of intestinal hormone that enhances nutrient induced insulin secretion.

They retard glucose entry into systemic circulation and lower post prandial glucose level.

Adverse drug reaction:

- Flatulence
- Abdominal discomfort
- Diarrhea occur in about 20% of patients. It is due to carbohydrates fermented by the flora of the large bowel.

Gastrointestinal side effect can be minimized by initiating therapy at a low dose with slow titration upward and symptoms diminish with continued use.

Drug Interaction:

- Gastrointestinal effect of acarbose is influenced by the drugs affecting gut motility.
- Cholestyramine increases the glucose lowering effect of acarbose.

Contraindication:

- Irritable bowel syndrome
- Severe kidney or liver dysfunction
- Inflammatory bowel disease
- Colon ulcer
- Partial intestinal obstruction
- Chronic intestinal disease

4.2.2.8. Amylin agonist:

Islet amyloid peptide (IAP) is a hormone secreted along with insulin by the β cell of pancreas in response to insulin secretagogues. It is found to be deficient in diabetics. IAP acts in the brain to:

- Reduce glucagon secretion from α cells
- Delay gastric emptying
- Retard glucose absorption
- Promote satiety

Pramlintide (Triptro-amylin) is an amylin analog and found to control blood sugar level. Studies have shown reduction in fructosamine which is a surrogate marker of hyperglycemia. Glycated haemoglobin reduction is around 0.5 to 1%.. It is found to produce significant weight loss.

Route of administration: Subcutaneous Injection

Adverse drug reaction: Nausea, vomiting

4.2.2.9. Sodium-glucose co-transport-2 inhibitor:

Glucose filtered at glomerulus is reabsorbed in proximal tubules by a major transporter SGLT-2 which induces glucosuria and lower blood glucose.

Dapagliflozin is SGLT-2 inhibitors and the adverse effects expected due to glycosuria are urinary and genital infections, electrolyte imbalance and increased urinary frequency.

4.2.3. Guidelines for management of DM:[18,34]

4.2.3.1. Canadian Diabetes Association (CDA) Practice Guidelines Expert Committee:

Type 1 DM

Initiated on Insulin immediately at diagnosis. In Intensive diabetes management the glycemic targets are achieved by administering basal bolus insulin regimens or Continuous Subcutaneous Insulin Infusion (CSII)

Hypoglycemia has to be minimized, glycated haemoglobin has to be Improve and post prandial glucose targets have to be achieved. Rapid acting bolus insulin analogues in combination with adequate basal insulin has to be used instead of regular insulin in these cases.

Type 2 DM

Initiation of anti hyperglycemic medication is required if glycemic targets are not achieved within 2 to 3 months of lifestyle management.

Antihyperglycemic must be added to attain targeted HbA1C within 3 to 6 months.

Patients with marked hyperglycemia (HbA1C > 8.5%) should be initiated preferably combination therapy one of which may be insulin. Therapy started concomitantly with life style management.

Metformin should be the initial drug of choice unless contraindicated. Additional antihyperglycemic agents are selected on the basis of:

1. Patient characteristics:

- Degree of hyperglycemia
- Presence of comorbidities
- Patient preference and ability to access treatment

2. Properties of the treatment:

- Contraindications to drug
- Glucose lowering effectiveness
- Risk of hypoglycemia
- Effectiveness in reducing diabetes complication
- Effect on body weight
- Side effects

Patients initiated with insulin or insulin secretagogues must be counselled about the prevention, recognition and treatment of drug-induced hypoglycemia

4.2.3.2. American Diabetes Association (ADA) Guidelines:

Type 1 DM

Most people with type 1 DM must be treated with multiple dose insulin (MDI) injection (3 to 4 injections per day of basal and prandial insulin) or CSII must be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose and anticipated activity

Type 2 DM

Preferred initial pharmacological agent for type 2 DM is metformin if not contraindicated and if tolerated. Newly diagnosed type 2 DM patients with elevated blood glucose levels or HbA1C consider insulin therapy with or without additional agents. If noninsulin monotherapy at maximum tolerated dose does not or achieve or maintain the HbA1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist or insulin. Patient-centred approach should be used to guide choice of pharmacological agents. Due to the progressive nature of type 2 DM, insulin therapy is eventually indicated for many patients with type 2 DM

4.2.4. Therapeutic uses:

- Type 1 Diabetes mellitus
- Type 2 Diabetes mellitus
- Polycystic ovarian syndrome
- Diabetic ketoacidosis
- Hyperosmolar coma

4.2.5. Recent advances:[35]

Currently available drugs for the treatment of DM do no cure this disorder. Symptoms return once the treatment is terminated. Development of novel drugs may bring about a change in the treatment modality.

i. D2 Dopamine agonist:

Bromocriptine activate the D2 dopaminergic receptors and alters hypothalamic control of insulin sensitivity in peripheral tissue. Taken early in the morning thought to act on hypothalamic dopaminergic control of circadian rhythm of hormone release and reset it to reduce insulin resistance. Reduction in glycated haemoglobin is around 0.5%.

Adverse drug reaction: Constipation, dyspepsia, abdominal pain, nausea, intestinal obstruction.

ii. β 3 adrenoreceptor agonist:

β 3 adrenoreceptor agonist showed marked selectivity for stimulation of lipolysis and hence for oxygen and energy consumption in skeletal muscle and adipose tissue. In certain type of fat cells, β cell activation induces the expenditure of metabolic calories as heat.

iii. Liver selective glucocorticoid antagonist

Glucocorticoids increase blood glucose level by antagonising the action of insulin. Glucocorticoid antagonist increase glucose disposal and inhibit hepatic glucose production by enhancing the action of insulin. Mifepristone is found to exhibit glucocorticoid antagonism.

iv. Glycogen synthase kinase 3 (GSK-3)

GSK-3 is a key enzyme involved in glycogen metabolism. It has been found to phosphorylate insulin receptor substrate. Lithium found to have insulin like effect by inhibiting GSK-3.

v. Selective inhibitors of Fructose 1, 6 bisphosphatase (FBPase)

Gluconeogenesis increases the endogenous glucose production. FBPase inhibitors may originate as a new class of antidiabetic drug by reducing gluconeogenesis.

vi. Anakinra

Interleukin 1 production is blocked by recombinant human interleukin-1receptor antagonist anakinra. Interleukin 1 β is released due to high glucose level which can reduce the function of β cell.

vii. Stem cell therapy

Effective in type 1 DM. Stem cells from cord blood found to restart the function of pancreas by reducing the need for insulin.

4.3. Drug utilization study:[36-44]

Drugs prescribed in clinical practice are mainly based on the evidence provided by the pre marketing and post marketing period. Data created from the post marketing period are needed to provide an adequate basis for improving drug therapy. Studies on drug utilization are a potential tool used to evaluate health systems. Tremendous improvement in the marketing of new

drugs, variation in the pattern of drug prescribed, delayed adverse effects and cost of drug as increased the importance of DUS.

The principal focus of DUS is to imply prescription of drug in an optimal dose on the right indication with the correct information and at an affordable price thereby facilitating rational use of drugs in a population. DUS contribute to rational drug use by increasing our understanding of how drugs are used, generate early signals of irrational use of drugs and enable us to intervene to improve drug therapy.

4.3.1. Definition:

"Drug utilization is defined as the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical, social and economic consequences."

4.3.2. Types of Drug use information:

1. Drug based information
2. Problem or Encounter-based information
3. Patient information
4. Prescriber information

4.3.3. Sources of drug utilization data:

Data's on drug utilization can be from:

- ❖ Medical practices
- ❖ Health facility
- ❖ Local manufacturer

- Whole sale dealers
- Drug importers

Drug utilization data can be obtained from quantitative and qualitative studies.

Quantitative studies describe the present state and trends in drug prescribing and drug use at various level of health care system. It is obtained from:

- Collected Data
- Surveys

Qualitative study assess appropriateness of drug utilization and link prescribing data to indications for prescribing. Quality indicators of drug use are:

- Average number of drugs per prescription
- Percentage of drugs prescribed by generic name
- Percentage of drugs prescribed from essential drug list
- Average cost of drugs per prescription

Data from medical practices can be used to generate indicators that provide information on prescribing habits. These indicators determine whether drug use problem exist. This can motivate health care providers to follow established health care standards

Databases currently available for purpose of DUS classified as:

- Non-diagnosis linked describe drug consumption in a population

- ❖ Diagnosis linked consider drug utilization linked to its indication and outcome

4.3.4. Instruments for data collection:

i. Patient files
ii. Computer registries
iii. Home inventories
iv. Questionnaires
v. Self reported data (subject to recall inaccuracy)

4.3.5. Objectives:

1. Ensuring that drug therapy meets current standards of care
2. Evaluating the effectiveness of drug therapy
3. Preventing medication related problems
4. Controlling cost of drug
5. Identification of areas of practice that require further education of practitioners
6. Identify problems and define areas for further investigation on the absolute and relative efficacy and safety of drug therapy
7. Suggest overuse, under-use or misuse of single drug compound or therapeutic classes of drugs
8. Aid in the determination of benefit risk and cost-effectiveness
9. Facilitate rational use of drug

4.3.6. Clinical importance:

Application of the theory of the evidence-based medicine into the everyday practice means critically appraising the evidence for validity and clinical usefulness. Data regarding drug use pattern can validate evidence-based practice and form the basis of decision making processes. There is a growing evidence that suboptimal use of drug including preventable drug related morbidity (PDRM) and mortality, is at least as costly as the prescription drug themselves. Drug utilisation study holds the promise that if implemented effectively it could partially address the problem by enhancing the appropriate use of drugs. Improved safe and effective drug use may restrain rising drug expenditure and by reducing PDRM, reduce hospital admission and other avoidable health care cost. Databases created as a result of DUR efforts have been used in new and innovative ways to incorporate health outcomes data and disease management interventions. Additional outcomes data, combined with quality assurance efforts, should increase the utility of DUR/disease management efforts in evaluating health systems while improving the effectiveness and efficiency of health care interventions.

4.3.7. Factors influencing drug utilization:

1. Population related factor: change in total population, change in population demographic, change in health status of a population
2. System related factor: change and transition associated with health system reform and restructuring changes in policies and programs
3. Research and technology related: new treatment approach

4. Pharmaceutical industry: development of new drug product, promotion of drugs to physician, drug sampling, direct to consumer advertising
5. Practice and people related: change in prescribing and dispensing practice

4.3.8. Uses of DUS:

i. Facilitate rational use of drug
ii. Increase our understanding of how drugs are being used
iii. Generate hypothesis that set the agenda for further investigation and thus avoid prolonged irrational use of drugs
iv. Assess whether interventions intended to improve drug use have had the desired impact
v. By comparing data from different localities may identify and promotion of best practice

4.4. Pharmacovigilance[45-50]

Pharmacovigilance is an important post-marketing tool in ensuring the safety of pharmaceutical product. It involves evaluating information gathered from the health care providers, pharmaceutical company and patients in order to understand the risks and benefits of a particular drug. These activities:

- ❖ Identify new information about adverse effects of the drug
- ❖ Prevent harm to the patient

Major role of pharmacovigilance is to identify and evaluate safety signals. Safety signal refers to concern about an excess of adverse events compared to that would be expected with a product use.

4.4.1. Terminology:

Pharmacovigilance:[47]

"Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects particularly long term and short term side effects of medicines."

Adverse event or adverse experience:[47]

An adverse event is an unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicinal product whether or not related to the medicinal product.

Adverse drug reaction:[47]

An ADR is a response to a drug which is noxious and unintended and which occurs at a dose normally used by man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.

Serious adverse event or serious adverse drug reaction:

A serious adverse event or reaction is any untoward medical occurrence that at any dose results in death or is life threatening. Life threatening refers to an event in which patient was at risk of death at the onset of event like:

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability
- Congenital anomaly or birth defect

4.4.2. History:

- 1986 Pharmacovigilance in India.
- 1997 India joined WHO adverse drug reaction monitoring programme based in Uppsala, Sweden.
- 2005 WHO sponsored and World bank funded National Pharmacovigilance programme in India.

4.4.3. Objectives:[48-50]

i. To monitor ADRs in Indian population
ii. To create awareness amongst health care professionals about the importance of ADR reporting in India
iii. To monitor benefit-risk profile of medicines
iv. Generate independent, evidence based recommendations on the safety of medicines
v. Support the centre for drug standard control organization (CDSCO) for formulating safety related regulatory decisions for medicines
vi. Communicate findings with all key stakeholders
vii. Create a national centre of excellence at par with global drug safety monitoring standards
viii. To keep in track the long term drastic effects of drug
ix. Contribute to the rational use of drug

4.4.4. Clinical importance:[50]

New drug released into market lack long term safety data. Prescribed drugs response varies due to interactions with drug and food. Awareness

about pharmacovigilance and practice according to it has a large impact on health care quality. Information on clinical, pathological and epidemiological information related to adverse reaction help us to fully understand adverse effects of drugs and for identifying patients at risk. ADR have the potential to provide insight into structure-activity relationship, pharmacokinetic, pharmacodynamic and genetic factors affecting the action of drugs. This may provide lead for other novel indications of the drug. Knowledge acquired following stringent monitoring on adverse effect of drug can prevent unnecessary suffering by patients and decrease financial loss of the patient due to inappropriate use of drug.

4.4.5. Current status in India:[48]

India is the fourth largest producer of pharmaceuticals in the World. Clinical trials involve lesser number and only a selected group of patients. Hence when drug enters the market less common adverse effects are not known. Benefit-risk ratio of pharmaceutical product is a dynamic variable and must be continuously monitored. Pharmacovigilance is in the stage of infancy in India.[8]

Most of the drug launched till date were already approved and marketed in other countries. Assessment of benefit-risk and appropriate changes were made from the experience gained from these markets. Hence pharmacovigilance was considered to be non-vital. Implementation of internal pharmacovigilance standards to detect adverse drug events cannot be ignored since the Indian drug companies started bringing their own research molecules.

Pharmacovigilance Programme of India (PvPI) was initiated by Government of India on 14th July 2010 with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National coordination centre for monitoring ADRs in the country for safe-guarding public health. 22 ADR monitoring centre was set up under this programme in the year 2010. On 15th April 2011 the National coordinating centre was shifted to the Indian Pharmacopoeia Commission, Ghaziabad, Uttar Pradesh.

4.5. Studies related to drug utilization of antidiabetic drugs:

Prescription pattern analyzed and the results published by *Olurishe et al*.[4] showed that number of drugs per prescription was 5.29. Large number of patients treated with combination of metformin and glibenclamide. Hypertension was found to be the commonest co-morbid disease.

In a retrospective study on adherence to OHA therapy was conducted by *Stephen et al*.[51] showed distribution of antidiabetic drugs were as sulphonylurea-66.4%, metformin-24.3%, troglitazone-6.6%, repaglinide-1.5% and α glucosidase inhibitor-1.1%.

Johnson et al.[52] studied utilization of diabetic medication for type 2 DM. Percentage of patients receiving antidiabetic therapy as monotherapy was 54.6%, oral combination therapy in 31.9% and oral with insulin combination therapy in 9.2% and remaining were on other antidiabetic drugs. Among monotherapy metformin in 24.6% was the most common and thiazolidinediones in 0.1% was the least prescribed drug for management of DM. 31.9% of prescription contained sulphonylurea with metformin which was

the highest percentage among the oral combination therapy. The least percentage of 0.3% were prescribed sulphonylurea with thiazolidinediones.

Study undertaken by *Rajeshwari et al*.[53] on DUS of antidiabetic drugs noted that majority of patients were on combination therapy of 71.87% and the remaining on monotherapy. Metformin was the most frequently utilized antidiabetic medication as monotherapy in 78.12% and the least was gliclazide in 6.25% of the study population.

In a cross sectional study conducted by *Upadhyay et al*.[54] observed that 51.27% of the diabetic patients were prescribed with biguanides.

Utilization of sulphonylurea group of agents showed a decreasing trend with a dramatic increase in prescription of biguanides in a study designed by *Yahaya et al*.[55] biguanides, sulphonylurea and α glucosidase inhibitors were prescribed in 51.3%, 48.5% and 0.2% respectively.

Study of utilization pattern by *Abdul et al*.[56] classified the antidiabetic medication prescribed as metformin (32%), glibenclamide (24.6%) and insulin (3.4%). Combination drug therapy prescribed were metformin with glibenclamide (28.6%), metformin with insulin (6.9%), metformin with glibenclamide and insulin (3%) and glibenclamide with insulin (1.5%).

Metformin was the monotherapy of choice prescribed in 32.2% in a study conducted by *Kannan et al*.[57] glimepiride was the sulphonylurea of choice as combination therapy with metformin in the same study.

Drug prescribing pattern for diabetes in a tertiary care hospital studied by *Akila et al*.[58] showed a drastic decline in glibenclamide prescription.

Metformin was the predominantly prescribed oral hypoglycemic agent both as monotherapy and combination therapy. There was a significant increase in the use of new antidiabetic agents like thiazolidinediones, α glucosidase inhibitor and DPP-4 inhibitor.

Lisha et al.[59] studied metformin to be the drug of choice as mono therapy and as combination therapy. Glipizide was found to dominate among the sulphonylurea. Pioglitazone was prescribed as combination therapy in few patients. Human insulin was the commonly prescribed insulin preparation.

In a prospective observational study conducted by *Sarumathy et al*.[60] antidiabetic were prescribed as monotherapy. Biguanides in 11.5% was found to be the most commonly prescribed antidiabetic drugs and least being α-glucosidase inhibitors in 6% of the study subjects. 20.6% were treated with combination of metformin and glibenclamide. Pre-mixed insulin (Human mixtard) was the commonly administered insulin preparation.

Jimoh et al.[61] study on pattern of antidiabetic use has shown the predominance of type 2 DM. Patients on combination therapy was higher. Insulin was frequently utilized antidiabetic medication among monotherapy.

In a cross sectional study conducted in North India by *Sharma et al*.[62] observed that the most prescribed antidiabetic drug was sulphonylurea (50.4%), followed by biguanides (46.6%) . Among sulphonylurea, glimepiride was the most prescribed and the least was glipizide.

Antidiabetic prescription evaluation study done by *Acharya et al*.[63] showed metformin to be the most frequently prescribed (40.45%) antidiabetic

drugs followed by glimepiride (28.39%), insulin(11.32%), voglibose(9.46%), pioglitazone(5.38%), repaglinide(1.86%), sitagliptin(1.30%), vidagliptin(0.37%) and glibenclamide(0.19%).

DUS in Tenali by *Kumar KS et al*.[64] showed insulin (65%) to be the most commonly utilized antidiabetic medication. Other drugs prescribed were metformin (54.2%), glimepiride (21%), glibenclamide (10%), glipizide (6.7%) and gliclazide (2.5%). Most commonly prescribed two drug combination therapies were glimepiride with pioglitazone (42.5%), insulin with metformin (16.6%), glimepiride with metformin (10%), glibenclamide with metformin (8.3%), glipizide with metformin (3.3%) and insulin with glimepiride (2.5%). Three drug combinations prescribed were insulin with glimepiride, metformin (8.3%) and glimepiride with pioglitazone, metformin (6.6%).

Study on prescribing pattern done by *Shahir et al*.[65] found out that percentage of participant receiving antidiabetic medicine according to the gender was 54.83% in male and 45.16% in female patient. The drugs prescribed were sulphonylurea (26.74%), glimepiride with metformin (18.60%), pioglitazone (13.56%), insulin (5.81%), insulin and other oral antidiabetic drugs (5.81%), glimepiride with pioglitazone, metformin (2.32%), glimepiride with pioglitazone (1.16%), sitagliptin (0.77%) and acarbose (0.77%). Insulin preparation used were human mixtard 30/70 penfil (30), human regular insulin (actrapid penfil) (10), NPH (isophane) pen (6), and insulin glargine pen (2).

Patel et al.[66] tabulated the antidiabetic medication prescribed as biguanides (87.7%), sulphonylurea (68.4%), insulin (22.8%), α glucosidase

inhibitors (21.1%), DPP-4 inhibitors (10.5%) and thiazolidinediones (10.5%). Antidiabetic combination drugs prescribed were glimepiride with metformin (50%), metformin with voglibose (7.02%), glimepiride with metformin, pioglitazone (7.02%), metformin with vildagliptin (3.51%), glibenclamide with metformin (1.75%) and sitagliptin with metformin (1.75%). Antidiabetic medication was prescribed as monotherapy (81.58%), two drug combination (65.78%) and three drug combination (7.02%). Classes of drugs prescribed were biguanides (40.35%), sulphonylurea (12.28%), α glucosidase inhibitors (16.67%), DPP-4 inhibitors (5.26%) and thiazolidinediones (7.02%). Average number of drugs prescribed per prescription was 7.58 $\pm$ 2.49. Percentage of drugs prescribed by generic name was 3.94%.

Jhaveri et al.[67] described antidiabetic utilization in geriatric population. Among the various drugs prescribed, antidiabetic medication included plain insulin (13.2%) and metformin (5.2%).

Observational study conducted in Eastern Nepal by *Das et al*.[68] in 2011 analysed the pattern of antidiabetic medication. Percentage of classes of drugs prescribed were biguanides (24.5%), sulphonylurea (19.9%), thiazolidinediones (3.6%) and insulin (2.5%). Number of drugs prescribed from each class were metformin (69), glimepiride (53), pioglitazone (10), soluble with isophane insulin (5), glipizide (3) and glargine insulin (2).

Guidoni et al.[69] analyzed the prescription pattern based on anatomical therapeutic group. Antidiabetic drugs prescribed as monotherapy were insulin (3.4%), glibenclamide (24.6%) and metformin (32%). Combination therapy prescribed were metformin with glibenclamide (28.6%), glibenclamide with

insulin (1.5%), metformin with insulin (6.9%) and metformin with glibenclamide and insulin (3.0%).

Kumar et al.[70] recorded the prescribing pattern in predesigned form and analysis revealed percentage of drugs prescribed as monotherapy were sulphonylurea (26.99%), insulin (17.18%), biguanides (14.1%) and α-glucosidase inhibitors (0.61%). As combination therapy drugs prescribed were metformin with human insulin (15.95%), human insulin (short acting and long acting), metformin with glibenclamide (5.52%), glimepiride with human insulin (3.68%) and metformin with glimepiride (1.84%). Drugs prescribed by generic name were minimum (14.59%) while maximum prescribed by brand name (85.08%).

Investigation of in-patient prescribing pattern of oral antidiabetic drugs in a tertiary care hospital by *Himanshu et al*.[71] declared the gender wise distribution as 57.5% in male and 42.5% in female. Drugs prescribed were metformin (43.8%), glimepiride (13.9%), glibenclamide (7.3%), metformin with glibenclamide (7.3%), metformin with gliclazide (5.8%), pioglitazone (5.1%), glipizide (2.9%), metformin with pioglitazone (1.5%) followed by metformin with glimepiride and pioglitazone (1.5%).

Taskeen et al.[72] study on rational drug prescribing pattern in geriatric patient, the most commonly prescribed drugs were antidiabetic medication (15.58%). Metformin was prescribed to maximum number of patient.

In *Willey et al*.[73] retrospective study, antidiabetic medication given as monotherapy were sulphonylurea (804), metformin (230), insulin (107) and thiazolidinediones (16). Among the combination drugs prescribed:

sulphonylurea with metformin (428), insulin with metformin (42), sulphonylurea with thiazolidinediones (41), metformin with thiazolidinediones (13), insulin with sulphonylurea (8), insulin with thiazolidinediones (7), sulphonylurea with α glucosidase inhibitor (2), sulphonylurea with other sulphonylurea (1) and metformin with meglitinide (1). Distribution of three drug combination were sulphonylurea, metformin with thiazolidinediones (52), two sulphonylurea with metformin (3) and metformin with thiazolidinediones (1).

Adla et al.[74] study showed metformin use in 68.75% and glibenclamide with metformin in the remaining of the diabetic patients studied during the analysis.

Gulam et al.[75] assessed oral hypoglycemic drug utilization in type 2 DM. Percentage of utilization pattern of antidiabetic drugs were metformin (34.5%), glimepiride (26.3%), pioglitazone (19.1%), miglitol (6.20%), vildagliptin (4.59%), gliclazide (2.2%), acarbose (1.93), voglibose (1.93%), sitagliptin (1.44%), rosiglitazone (1.2%) and glipizide (0.5%). Percentages of patients receiving antidiabetics as monotherapy were maximum with biguanides (10.9%) and minimum with thiazolidinediones (1.1%) and DPP4 inhibitors (1.1%). Maximum percentage encountered with various of patients receiving as 2 drug therapy were glimepiride with metformin (13.04 %), as 3 drug therapy were glimepiride with metformin, pioglitazone (23.9%) and as 4 drug therapy were glimepiride with metformin, pioglitazone, miglitol (8.2%).

Rajkumar et al.[76] observed the drug use pattern among type 2 diabetics which was found to be more among females (51.66%) than males (48.34%) and type 1 includes 66.67% in male and 33.33% in female.

Prescribed pattern of different antidiabetic drugs as monotherapy in percentage were glimepiride (36.8%), metformin (31.4%), pioglitazone (8%), insulin (7.8%), gliclazide (4.8%), voglibose (4%) and vildagliptin (1.6%). Metformin was given as a combination therapy with glimepiride (6.4%), gliclazide (3.2%) and pioglitazone (0.8%). A combination of glimepiride, metformin and pioglitazone was given in 4% of the patient.

In a cross sectional retrospective study done by *Hasniza et al*.[77] revealed that insulin was the most common antidiabetic prescribed. The most common combination therapy was oral hypoglycemic with insulin (17.5%). Most frequently used oral antidiabetic were biguanides, sulphonylurea followed by acarbose and sitagliptin.

Prescription in type 2 DM in tertiary care hospital by *Sharma et al.*[78] studied that 77% of the drugs were prescribed as monotherapy. Metformin was advised as monotherapy in 31.72% of the patients. Other drugs prescribed as monotherapy were glimepiride, glibenclamide, voglibose, pioglitazone, insulin, sitagliptin and vildagliptin.

Sutharson et al.[79] gave details on percentage of drugs prescribed at diabetic OPD as glibenclamide (47.4%), metformin (38.1%), glipizide (24.9%), lente insulin (5.6%), insulin porcine mixture (5.5%), regular insulin (5.2%) and tolbutamide (1.4%).

Okonta et al.[80] conducted a study to evaluate prescription pattern of antidiabetic and antihypertensive medication in Nigeria. Patients name was mentioned only in 93.4% of the prescription. Gender wise distribution of drug use pattern were studied which showed a majority of prescription for females

(55.1%) than males (44.9%). Drugs prescribed by generic name were 38.7% and by trade name were 61.3%. Classes of antidiabetic drugs prescribed were biguanides (42.3%), sulphonylurea (26.2%), combination of sulphonylurea with biguanides (20.2%), insulin (10.7%) and thiazolidinediones (0.6%).

A study done on prescribing pattern of antidiabetic drugs by *Vengurlekar et al*.[81] categorised use of prescribed drugs as biguanides (27%), sulphonylurea (22.60), glitazones (13.90%), miglitol (8.69%) and insulin (4.5%). Most commonly prescribed combination therapy was metformin with glimepiride (20.86%) followed by pioglitazone with glimepiride (4.34%) and pioglitazone with metformin (2.6%). 51 to 60 year of age were commonly affected followed by 41 to 50 years. Majority of affected population were male (66.36%) and was lesser among females (33.64%).

Alam et al.[82] study on drug utilization pattern in New Delhi identified that 37% of the diabetic patients were advocated with metformin, 31.9% with sulphonylurea, 24.8% with thiazolidinediones and α glucosidase inhibitors in 6.3% as monotherapy.

Dhwani et al.[83] studies on prescribing trends in diabetic patients analyzed 492 data out of which 67.88% were males and 32.11% were females. Percentage of antidiabetic medication prescribed were metformin 76%, insulin 35%, gliclazide 31.50%, pioglitazone 25.60%, glimepiride 24.60%, acarbose 16.10%, glipizide 13.40%, rosiglitazone 10.20% and glibenclamide 4.70%. Combination of antidiabetic prescribed were insulin with metformin (12.8%), metformin with glimepiride (8.7%), metformin with

gliclazide, pioglitazone (7.9%), insulin with gliclazide (5.9%) and gliclazide with metformin (5.5%).

In a comparative study of drug use pattern conducted by *Garg et al*.[84] revealed that 79.6% in retrospective and 43.4% in prospective were found to be treated with antidiabetic drugs. The most commonly prescribed drugs were sulphonylurea (39.7% in retrospective and 22.8% in prospective) followed by biguanides (21.5% in retrospective and 13% in prospective) and insulin (9.2% in retrospective and 4.8% in prospective).

Suleiman et al.[85] prescription analysis in Sharjah General hospital showed that among the various drugs prescribed 19.49% were antidiabetic drugs. Most commonly prescribed antidiabetic drugs were metformin (58.71%) and the least were glimepiride (4.98%). Gliclazide were prescribed in 34.33% of the analysed data.

A gender based antidiabetic survey done by *Raj et al*.[86] revealed that type 2 DM predominate. Metformin was the preferred antidiabetic among monotherapy prescribed to 30% of the patients. Most frequently prescribed combination therapy was glibenclamide with metformin in 27%.

Stavros et al.[87] observed the antidiabetic drug treatment in Greek patients. Percentage of study population prescribed with oral antidiabetic drugs were 56.5% and 42.6% with insulin. Oral antidiabetic drugs prescribed were metformin (80.4%), DPP-4 inhibitor (34.5%), sulphonylurea (26.6%), thiazolidinediones (4.9%), GLP-1 agonist (3.8%), glinide (2.7%) and acarbose (2.2%).

Observation of prescription pattern by *Yusefzadeh et al*.[88] revealed that biguanides (61.7%) was the most often prescribed antidiabetic medication. Other drugs prescribed less frequently were sulphonylurea (59.9%), α-glucosidase inhibitors (4.5%), repaglinide (2.7%) and thiazolidinediones (0.7%). Insulin was given as monotherapy in 23.7% and as combination therapy with oral antidiabetic drugs in 6.8%. Oral antidiabetic medication as monotherapy was prescribed in 69.5%. Among the various classes of drugs metformin (61.7%) and glibenclamide (59.9%) were the most commonly prescribed antidiabetic drugs. 30.5% of the prescription included insulin preparation. Insulin preparation commonly prescribed were NPH with regular insulin (20.7%), NPH (4.5%), insulin aspart (3.6%), regular (0.9%), insulin glargine (0.6%), lansulin N (0.2%). Most frequently prescribed combination therapy were metformin with glibenclamide (41.5%). This study also identified the common co-morbid condition like hypertension, angina pectoris and hyperlipidemia to be associated with DM.

Knox et al.[89] study on antidiabetic drug utilization in pregnant women showed a steady increase in the use of metformin and sulphonylurea. Most commonly prescribed antidiabetic drugs were insulin, metformin, sulphonylurea and thiazolidinediones.

Study about utilization pattern of antidiabetic medication was done by *Dave et al*.[90] Oral antidiabetic drug prescribed as single and combination therapy were 14.83% and 68.82% respectively. Percentage of oral antidiabetic drugs in combination with insulin was 16.55%. Combination therapy prescribed were glipizide with metformin (38.42%), glipizide with metformin and pioglitazone (15.17%), metformin with glimepiride and

pioglitazone (3.45%), glipizide with pioglitazone (2.76%), metformin with glimepiride (2.76%), metformin with pioglitazone (1.38%), acarbose with glipizide and metformin (1.38%) and gliclazide with pioglitazone (1.38%). Other less commonly prescribed antidiabetic combination therapy (1.72%) were glipizide either with repaglinide, rosiglitazone, metformin or glimepiride and pioglitazone with glimepiride.

Outpatient utilization of antidiabetic drugs was studied by *Adibe et al*.[91] Antidiabetic drugs frequently prescribed were metformin (38.6%), glibenclamide (27.9%), chlorpropamide (13.4%), fast acting insulin (9.9%), intermediate-acting insulin (6.8%) and rosiglitazone (4.4%).

A prospective study on drug utilization of oral hypoglycemic therapy in type 2 DM was done by *Khan et al*.[92] Classes of antidiabetic drug prescribed were biguanides in 34.5%, sulphonylurea in 28.9%, thiazolidinediones in 20.3%, α glucosidase inhibitors in 10.14% and DPP-4 inhibitors in 6.03%. Percentage of individual drugs prescribed were metformin in 34.5%, glimepiride in 26.3%, pioglitazone in 19.1%, miglitol in 6.20%, vildagliptin in 4.59%, gliclazide in 2.2%, voglibose in 1.93%, acarbose in 1.93%, sitagliptin in 1.44%, rosiglitazone in 1.2% and glipizide in 0.5%.

Abassi et al[93] study on current prescribing pattern of antidiabetic drugs revealed that metformin was the most frequently advocated by the treating physician. The other drugs prescribed were sulphonylurea in 30.68%, insulin in 21.96%, thiazolidinediones in 9.12% and DPP-4 inhibitors in 1.65%.

4.6. Studies related to adverse drug reactions of antidiabetic drugs:

Pharmacovigilance study done by *Himanshu et al*.[46] identified 122 reports of ADRs due to different groups of drugs out of which 10.7% were due to antidiabetic therapy.

Saravanan et al.[94] identified that male were predominantly reported ADRs due to administration of antidiabetic medications. The above study reported hypoglycemia, vomiting, giddiness, abdominal distension, diarrhea, sweating, edema, gastric irritation and headache in the study population. The same study also revealed that the incidence of adverse drug reactions were in the higher side in patients treated with glimepiride compared to metformin, pioglitazone and combination of glimepiride with metformin.

Monitoring of ADRs in a tertiary care teaching hospital by *Kathiria et al*.[95] identified that hypoglycemia due to insulin was 3.33%. Among the various ADRs reported 13.33% were due to antidiabetic medication.

Sharma et al.[96] analysed 465 vigiflow data on ADR associated with antidiabetic medication and identified the gender distribution to be 273 in male and 182 in female. Number of patients reported ADR were 218 with insulin, 74 with metformin, 41 with glimepiride, 36 with glibenclamide, 33 with glitazone, 22 with glipizide, 5 with acarbose, 2 with human actrapid and 2 with DPP-4 inhibitors. Other system affected following use of antidiabetic were classified as metabolic and nutritional in 279, gastrointestinal system disorders in 78, central and peripheral nervous system disorders in 40, skin and appendage disorder in 30, general disorder in 16, psychiatric disorder in 4, respiratory system disorder in 2, special senses in 2, heart rate and rhythm disorder in 2,

vascular disorder in 2, cardiovascular disorder in 2, liver and biliary system disorder in 1 and vision disorder in 1.

An analysis was done on medication use leading to emergency department visits for ADR in older adults by *Daniel et al*.[97] Most common antidiabetic medication implicated to cause ADR in decreasing order were 13% with insulin, 2.3% with metformin, 2.2% with glyburide and 1.5% with glipizide.

Budnitz et al.[98] studied medication use leading to emergency department visits due to adverse drug events in older adults. Number of patients reported with ADR due to DM treatment was 616 with Insulin, 103 with metformin, 98 with glyburide and 57 with glipizide.

Hypoglycemia was the frequently noticed ADR in 18 diabetic patient during a study on adverse effects of antidiabetic medication by *William et al*.[99] Patient encountered with hypoglycemic episode were on sulphonylurea.

4.7. Studies related to pharmacoeconomic study of antidiabetic drugs:

In a pharmacoeconomic analysis conducted by *Upadhyay et al*.[54] found out that cost per prescription for insulin was 41.07% and it was 32.60% for biguanides of the total cost encountered.

In a study conducted by *Kannan et al*.[57] average cost of therapy per prescription for one month was Rs 783.55. Cost of antidiabetic therapy for one month was less than Rs 600 in 79 prescriptions, Rs 601 to 1200 in 99, Rs 1201 to 1800 in 19, Rs 1801 to 2400 in 4 and more than Rs 2401 in 1 prescription.

In an observational study conducted by *Sarumathy et al*.[60] the average prescription cost was Rs 65.26 per 5 days for treating DM.

Jhaveri et al.[67] did pharmacoeconomic analysis in geriatric population on antidiabetic therapy. Total cost of treatment was found to be 665.

Pharmacoeconomic study of antidiabetic drugs was studied by *Adibe et al*.[91] and showed that cost of DM therapy to be rosiglitazone = 160.7, fast acting insulin = 108, intermediate-acting Insulin = 98.5, metformin = 57.1, chlorpropamide = 26.3 and glibenclamide = 10.7.

Asseffa et al.[100] analyzed the cost of therapy with antidiabetic medication. Percentages of total drug cost were 88.19 with Insulin, 5.26 with metformin and 0.97 with glibenclamide.

Materials and Methods

5. Materials and methods:

5.1. Study design:

This study was designed a cross sectional study.

5.2. Study setting:

This study was conducted at OPD of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari District, Tamil Nadu.

5.3. Study period:

This study was done during the period August 2013 to August 2014.

5.4. Inclusion criteria:

1. DM patients attending the Medicine OPD
2. DM patients with or without other co-morbid conditions.
3. Both gender affected with DM
4. Patients with type 1 or type 2 DM

5.5. Exclusion criteria:

Patients attending the Medicine OPD for re-fill of antidiabetic drugs who have been given the recruitment number

5.6. Parameters:

i. Study participants receiving antidiabetic drugs as monotherapy

ii. Study participants receiving antidiabetic drugs as combination therapy

iii. Study participants receiving antidiabetic drugs as combination therapy

iv. Classes of antidiabetic drugs with most expensive and least expensive

v. Adverse drug reactions experienced in patients prescribed with antidiabetic drugs

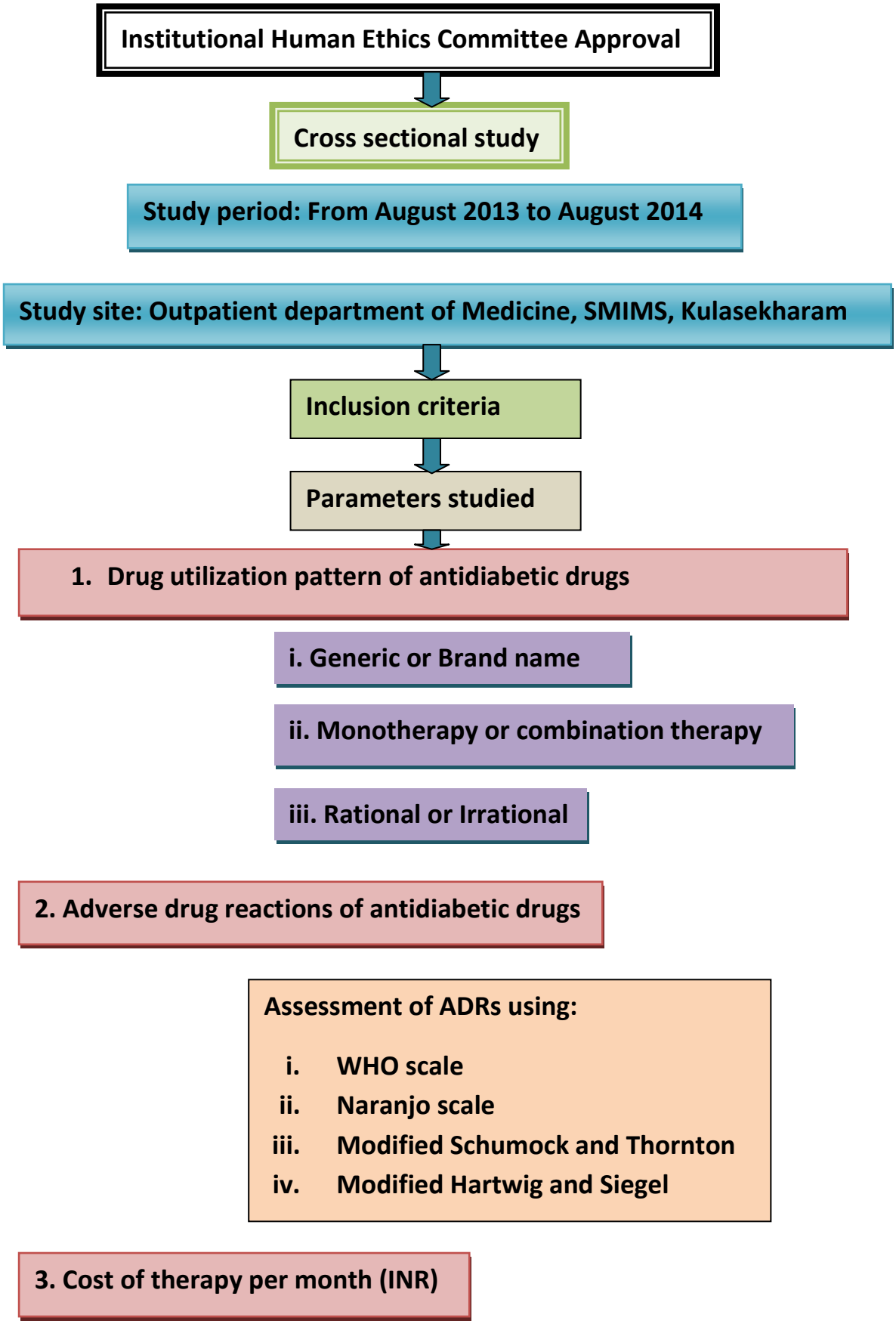
5.7. Institutional Human Ethics Committee Approval:

The study proposal was submitted to Institutional Human Ethics Committee (IHEC) of Sree Mookambika Institute of Medical Sciences (SMIMS), Kulasekharam, Kanyakumari District, Tamil Nadu for approval and the research proposal was approved by the IHEC of SMIMS with Ref. No. **SMIMS/IHEC/2013/A/21**. The certificate of approval for the same has been enclosed in annexure.

5.8. Procedure:

The study was conducted in collaboration with the Department of Medicine. Study subjects who were diabetic either with or without other co-morbid condition were recruited according to the inclusion and exclusion criteria from the Outpatient Department of Medicine. Informed written consent was obtained from each study subject. Details of each study subject was recorded in a predesigned case record form. Prescribed antidiabetic drugs details including formulation, dose, frequency, duration, route of administration and whether taken before or after food was noted in the case record form. Cost of antidiabetic therapy for a period of one month was calculated.

Figure 5: Flow chart showing the methodology of the study



Study subjects were enquired regarding presence of other co-morbid condition and if so drugs prescribed for the same was noted. Enrolled study participants were interviewed regarding experience of any adverse effect following initiation of antidiabetic therapy. If yes, ADR experience details will be filled up in the CDSCO ADR form.

5.9. Method of analysis:

Data obtained from case record form will be presented as:

i. Percentage of study participants receiving antidiabetic drugs as monotherapy.

ii. Percentage of study participants receiving antidiabetic drugs as combination therapy.

iii. Percentage of participants receiving different

- Classes of antidiabetic drugs like sulphonylureas, biguanides, thiazolidinediones
- Classes of antidiabetic drugs which will be more expensive and least expensive
- Causality assessment of adverse drug reactions reported in patients prescribed with antidiabetic drugs by using
    i. WHO Causality assessment
    ii. Naranjo algorithm
    iii. Modified Schumock and Thornton
    iv. Modified Hartwig and Siegel

i. WHO Causality assessment[101]

This assessment scale was put forth by the World Health organisation collaborating centre for International Drug Monitoring, the Uppsala Monitoring centre (WHO-UMC). Suspected adverse drug reactions due to drugs are combined assessment taking the case history and quality of documentation of observation.

Table No 7: WHO causality assessment scale

Assessment criteria	Causality category
➢ **Adverse event or laboratory abnormality occurring in a plausible time relationship to drug intake** ➢ **Cannot be explained by disease or other drugs** ➢ **Response to withdrawal** ➢ **Satisfactory rechallenge**	**Certain**
➢ **Adverse event or laboratory abnormality occurring in a plausible time relationship to drug intake** ➢ **Cannot be explained by disease or other drugs** ➢ **Response to withdrawal** ➢ **Rechallenge is not required**	**Probable/Likely**
➢ **Adverse event or laboratory abnormality occurring in a plausible time relationship to drug intake** ➢ **Can also be explained by concurrent disease or other drugs** ➢ **Lack information on drug withdrawal**	**Possible**

➢ **Adverse event or laboratory abnormality occurring in a temporal relationship to drug intake** ➢ **Causal relationship is improbable**	**Unlikely**
➢ **Adverse event or laboratory abnormality reported** ➢ **More data essential for proper assessment**	**Conditional/ Unclassified**
➢ **Adverse event reported cannot be assessed because of-** ▪ **Insufficient information or** ▪ **Contradictory**	**Unassessible/ Unclassifiable**

ii. Naranjo algorithm[102]

Naranjo Probability Scale assesses unexpected ADRs. It is helpful for evaluators with little experience.

Table No 8: Naranjo algorithm scale

Questions	Yes	No	Do not know
Any previous conclusive report on this reaction?	+1	0	0
Did the adverse event appeared soon after the administration of suspected drug?	+2	-1	0
Was there an improvement in adverse reaction after the drug was discontinued or when specific antagonist was administered?	+1	0	0
When the drug was discontinued did the adverse reaction reappear?	+2	-1	0

Is there any alternative reason that could have caused the reaction?	-1	+2	0
Whether reaction reappeared when a placebo was given?	-1	+1	0
Whether drug was detected in the blood in a concentration known to be toxic?	+1	0	0
Severity of reaction – is it more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient experience similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

Category is defined by calculating the total score from this table as:

1 to 4 :Possible

5 to 8 :Probable

More than 9 :Definite

iii. Modified Schumock and Thornton[102,103]

Define various criteria to determine preventability of an ADR.

Section A

1. History of allergy or previous reaction to the drug
2. Inappropriate drug for patient's clinical condition
3. Dose, route or frequency of drug administration inappropriate for the patient's age, weight or disease state
4. Documentation of toxic serum blood concentration
5. Treatment known for the adverse drug reaction

Answering yes to one or more of the above questions implies that an ADR is **Definitely** preventable. If answer is no then proceed to next section.

Section B

1. Required therapeutic drug monitoring not performed
2. Any drug interaction involved in the ADR
3. Poor compliance involved in the ADR
4. Preventive measures not prescribed or administered to the patient

Answering yes to one or more of the above questions implies that an ADR is **Probably** preventable. If answer is no then proceed to next section.

Section C

If answers are negative to section A and B then the ADR is **Not preventable**

iv. Modified Hartwig and Siegel[102,103]

Severity of ADR can be assessed using this scale.

ADR is **Mild** if it requires:

- Level 1: no change in treatment with the suspected drug (or)

- Level 2: suspected drug to be withheld or changed, no antidote required, no increase in length of stay

ADR is **Moderate**:

- Level 3: If it requires suspected drug to be withheld or changed, antidote or other treatment is required, no increase in length of stay (or)
- Level 4(a): Any level 3 with increase in length of stay by at least one day (or)
- Level 4(b): If ADR is the reason for admission

ADR is **Severe**:

- Level 5: Any level 4 that requires intensive care treatment (or)
- Level 6: Permanent harm to the patient (or)
- Level 7: Directly or Indirectly leads to death of the patient

Results

6. Results:

6.1. Demographic characteristics:

The demographic profile of 169 diabetic patients is given in table no 9.In the current study the age group commonly affected was found to be between the 61 to 70 years. Gender wise distribution of diabetic patients shows predominance among the female patient accounting 111 prescriptions and remaining being male. The mean weight of diabetic patients accounted during the study was 67.56 kg. Average height of the diabetic patients in this study was 155 cm. Body mass index was calculated as mean and was found to be 27.82 kg/m^2.

6.2. Clinical presentation of diabetes mellitus:

Patients attending the diabetic OPD during the study period were with type 2 DM alone. Among them known case of DM were 146 and the newly diagnosed patients were 23 only as shown in table no 10.

6.3. Co-morbid conditions associated with diabetes mellitus:

In this study systemic hypertension was the most frequently associated co-morbid condition as shown in table no 11. The other less common co-morbid conditions were chronic obstructive pulmonary disease (COPD), dyslipidemia, thyroid disorder, benign prostatic hypertrophy (BPH), cardiovascular disorder and depression.

6.4. Antidiabetic drugs prescribed by generic name and brand name:

The pie diagram represented in figure 6 give details of antidiabetic drugs as prescribed by the physician. Out of 192 drugs prescribed, more percentage of drugs was prescribed by brand name and drugs prescribed by trade name were only 13%.

6.5. Prescription as monotherapy and combination therapy:

Figure 7 depicts the prescribing of antidiabetic drugs as a single therapy or combination therapy. Managing DM with more than two drugs was advocated for 73% of the patients and the remaining being with one drug.

6.6. Prescription as combination therapy:

Various numbers of drugs prescribed in combination therapy is shown in figure 8. Majority of patients were prescribed with 2 drug combination therapy and the remaining with 3 drugs and 4 drug combination therapies.

6.7. Antidiabetic drugs prescribed as monotherapy:

Bar diagram in figure 9 depicts the drugs used as monotherapy. Frequently utilized drug as monotherapy was metformin, prescribed in 13 patients. DM treated in 12 with insulin, 7 with pioglitazone, 4 with glimepiride, 4 with voglibose, 3 with gliclazide and the rest with glibenclamide.

6.8. Antidiabetic drugs as 2 drug combination therapy:

Figure 10 representing the drugs used in 2 drug combination therapy. 80 prescriptions contained a combination of glimepiride and metformin which is the highest among the 2 drug combination therapy. Metformin was prescribed with glipizide in 14, glibenclamide in 2, pioglitazone in 2, voglibose in 2 and insulin in 2. Pioglitazone was prescribed in two patients either with glimepiride or glipizide.

6.9. Antidiabetic drugs as 3 drug combination therapy:

Glimepiride, metformin and pioglitazone was most commonly accounted in 5 prescriptions among the 3 drug combination therapy. Glimepiride and metformin was prescribed with insulin in 3, voglibose in 2, acarbose in 2 and glibenclamide in 1. Pioglitazone and metformin was given in combination with sulphonylurea group (glibenclamide, glipizide or gliclazide) in 3 patients. One prescription contained a combination of glimepiride, metformin and sitagliptin as viewed in figure 11.

6.10. Adverse drug reaction reported due to antidiabetic drugs:

ADRs reported following treatment of DM with OHA and insulin is shown in figure 12. ADRs shows hypoglycemia in 20, abdominal discomfort in 11, nausea with vomiting in 9, diarrhea in 7, edema in 6, headache in 6, myalgia in 5, rashes in 4, weight gain in 3, metallic taste in 3 and pruritis in 2.

6.11. ADRs reported with monotherapy:

Maximum of 14 ADRs were reported with insulin. Drugs producing ADRs less frequently were thiazolidinediones, biguanides, sulphonylureas and alpha glucosidase inhibitors is represented in figure 13.

6.12. ADRs with combination therapy:

Combination of drugs producing ADRs are shown in figure 14. 30 ADRs were reported due to combination antidiabetic therapy out of which 28 were due to sulphonylureas with biguanides and the remaining was due to sulphonylureas with biguanides and thiazolidinediones.

6.13. Causality assessment using WHO scale:

64%of ADRs were probable, 16% possible, 7% conditional, 5% unclassifiable, 4% unlikely and rest certain as depicted in figure 15.

6.14. Causality assessment using Naranjo algorithm scale:

Category of ADR according to the causative relationship to the drug administration is shown in the figure 16. Naranjo algorithm scoring categorised ADRs to be possible in 92% of the report. The remaining was probable and definite.

6.15. Preventability of ADR using Modified Schumock and Thornton scale:

ADR was found to be definitely preventable in 19% of the reports. It was only probably preventable in 18% and not preventable in the remaining as seen in figure 17.

6.16. Severity of ADR using Modified Hartwig and Siegel scale:

Severities of ADRs reported were mild in 75% of the patients. Remaining was moderate and no severe ADRs were reported as shown in figure 18.

6.17. Pharmacoeconomics of antidiabetic drugs as monotherapy:

Cost of therapy per month in Indian rupee (INR) for oral antidiabetic drugs prescribed in generic and brand name are individually represented as bar diagram in figure 19. Pharmacoeconomic evaluation shows that cost of therapy was higher with branded drugs while comparing with the generic equivalent.

6.18. Pharmacoeconomics of antidiabetic therapy as fixed dose combination:

Fixed dose combination with 3 drugs was more expensive compared to combination with 2 drugs. Cost per month in INR for combination therapy used in this study is given in figure 20.

6.19. Pharmacoeconomics of insulin preparation:

Cost per unit of insulin preparation utilized in this study is represented as bar diagram in figure 21.

Table No. 9: Demographic profile of the diabetic patients on antidiabetic therapy

S. No	Demographic characters		Number	Percentage (%)
1.	Age (years)	31 to 40	8	5
		41 to 50	34	20
		51 to 60	54	32
		61 to 70	58	34
		71 to 80	11	7
		81 to 90	4	2
2.	Sex	Male	58	34.31
		Female	111	65.6
3.	Weight (kg)		67.56±14.17*	
4.	Height (cm)		155±0.04*	
5.	BMI (kg/m^2)		27.82±5.05*	

BMI: Body mass index
***Values are expressed in Mean±SD
SD: Standard Deviation

Table No. 10: Distribution of patients according to clinical presentation

S. No	Clinical presentation		n	%
1.	Type of DM	Type 1	0	0
		Type 2	169	100
2.	DM presented as	Known case	146	86.39
		Newly diagnosed	23	13.61

n: Number
%: Percentage

Table No. 11: Number and percentage of co-morbid conditions associated with DM

S. No	Co-morbid condition	n	%
1.	Systemic hypertension	62	71
2.	Chronic obstructive pulmonary disease (COPD)	7	8
3.	Systemic hypertension with COPD	6	7
4.	Dyslipidemia	3	4
5.	Hypothyroidism	3	4
6.	Benign prostatic hypertrophy	2	2
7.	Cardiovascular disorder	1	1
8.	Hyperthyroidism	1	1
9.	Systemic hypertension with dyslipidemia	1	1
10.	Depression	1	1

n: Number
%: Percentage

Figure-6: Pie diagram showing number of antidiabetic drugs prescribed by generic name and brand name

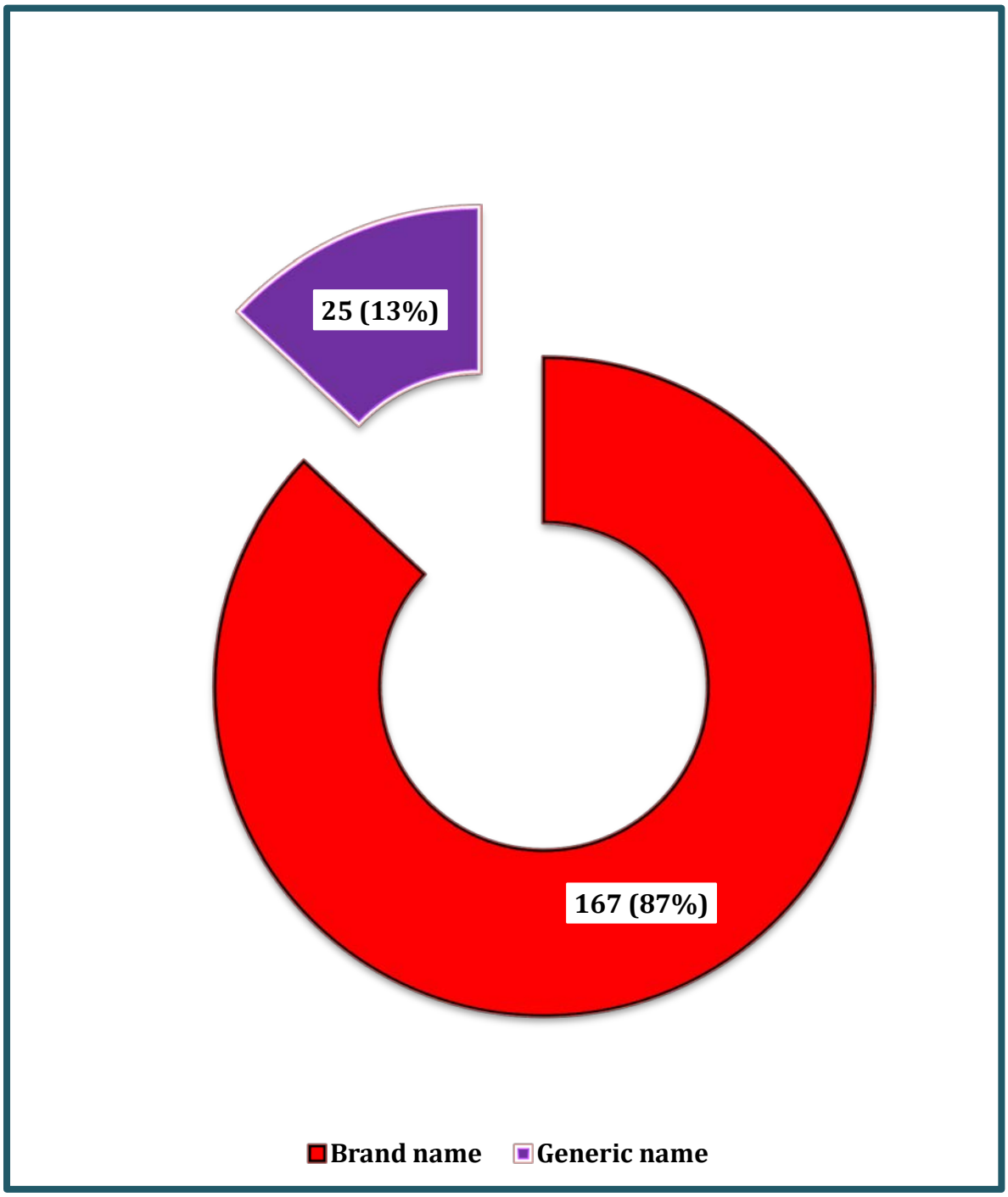


Figure-7: Pie diagram showing percentage of prescription of antidiabetic drugs as monotherapy and combination therapy

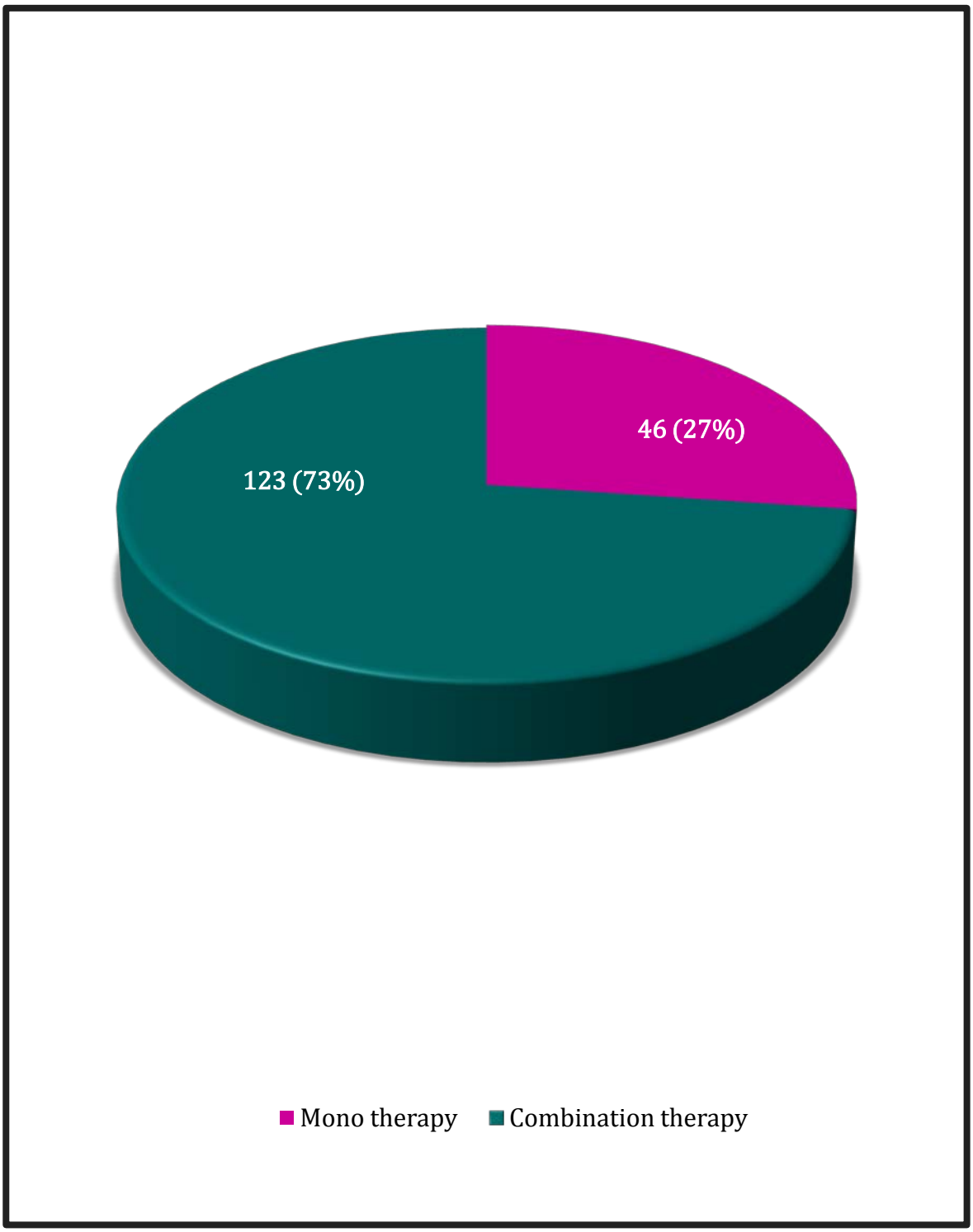


Figure-8: Pie diagram showing the percentage wise distribution of antidiabetic drugs as combination therapy

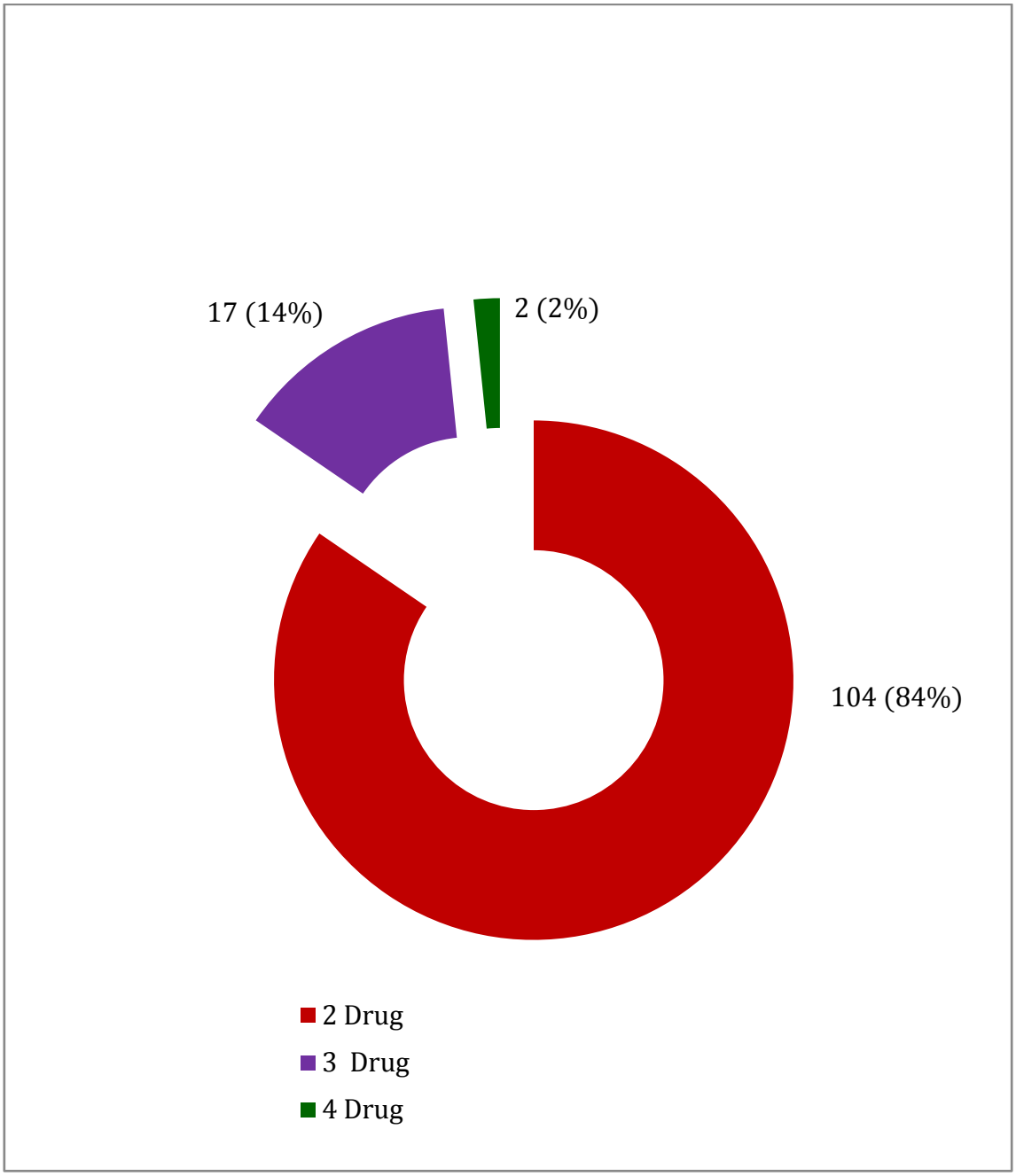


Figure-9: Bar diagram showing the number of prescriptions of antidiabetic drugs as monotherapy

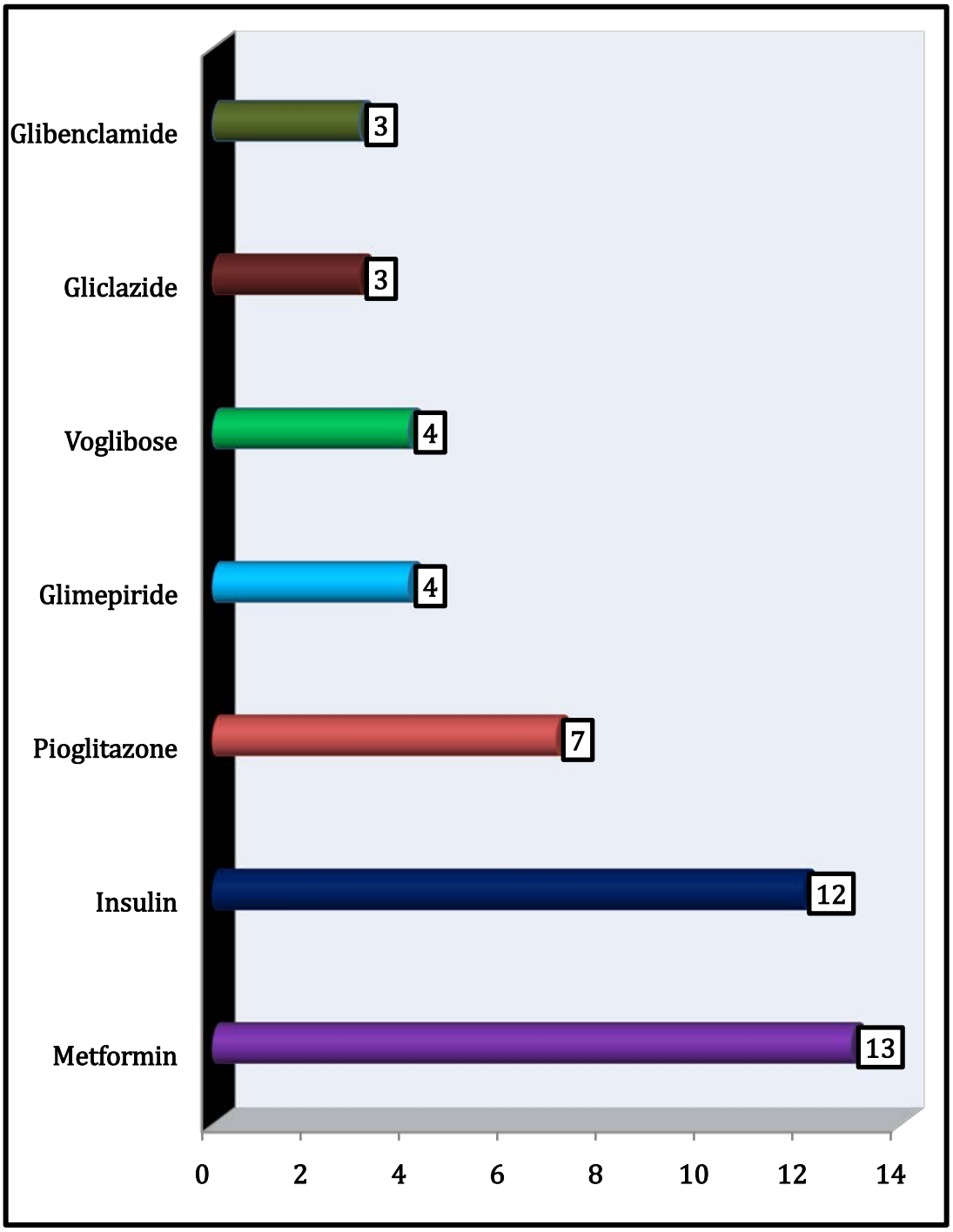


Figure-10: Bar diagram showing the number of prescriptions of antidiabetic drugs as combination of 2 drugs

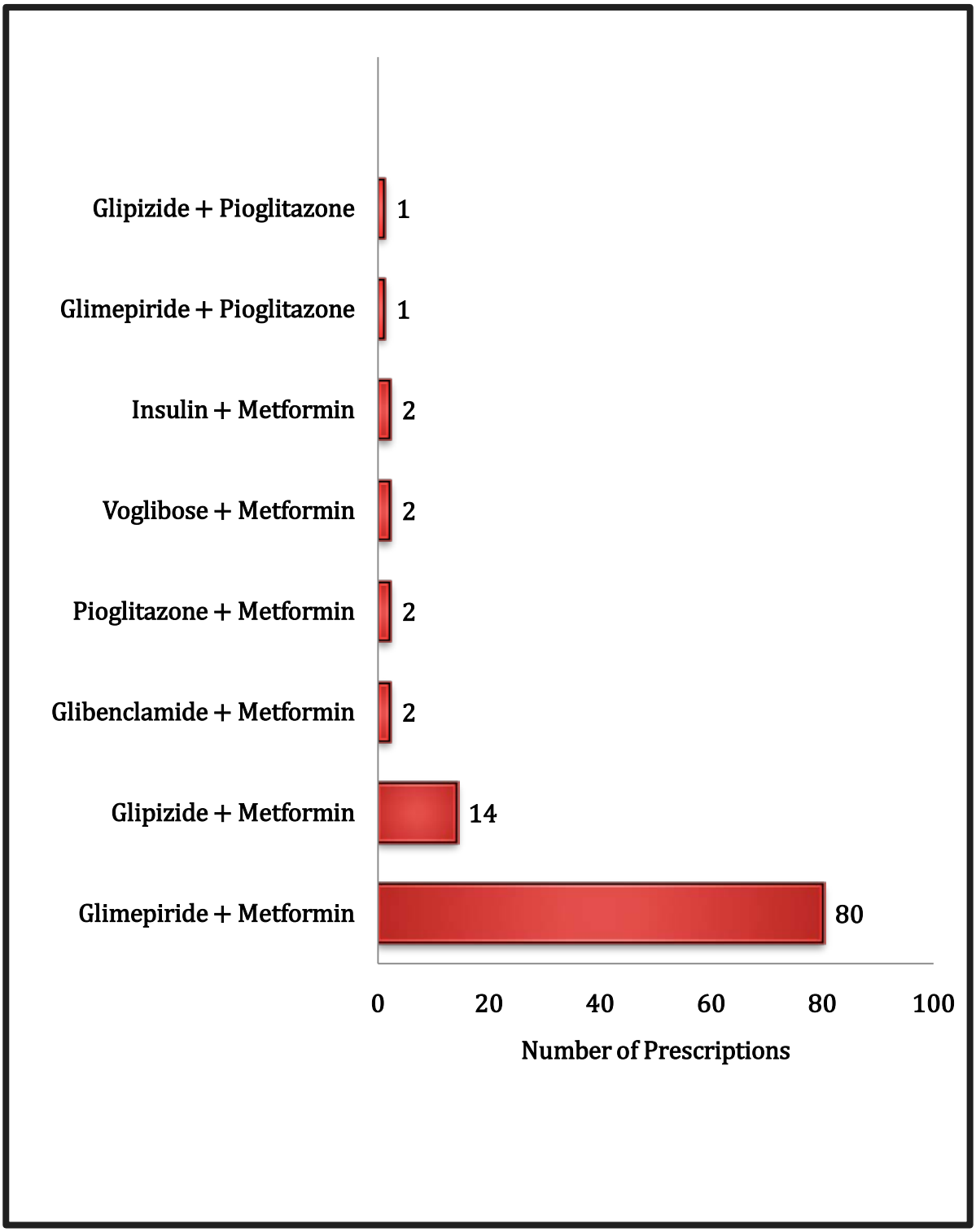


Figure-11: Bar diagram showing the number of prescriptions of antidiabetic drugs as combination of 3 drugs

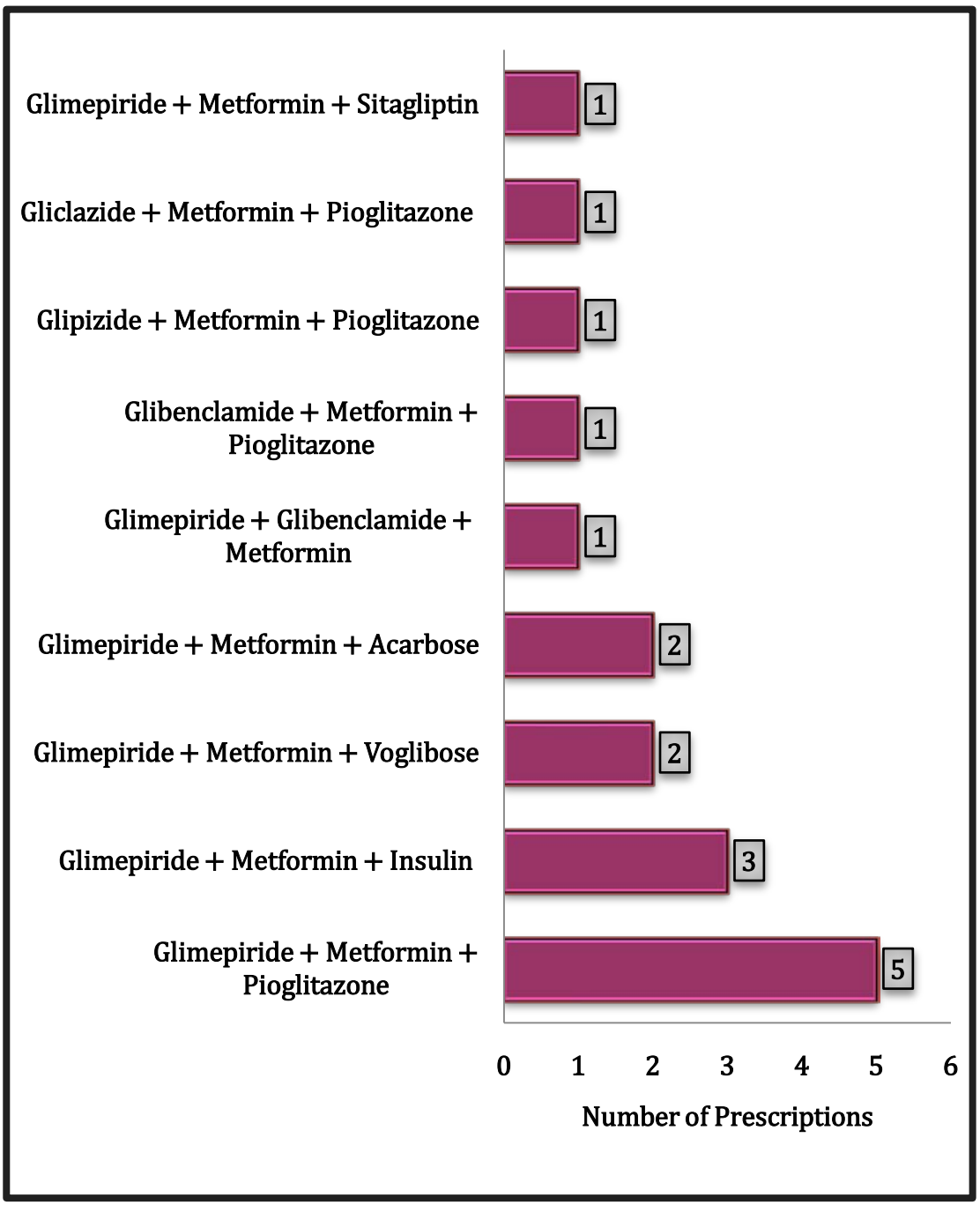


Figure-12: Bar diagram showing the adverse drug reactions reported due to antidiabetic drugs

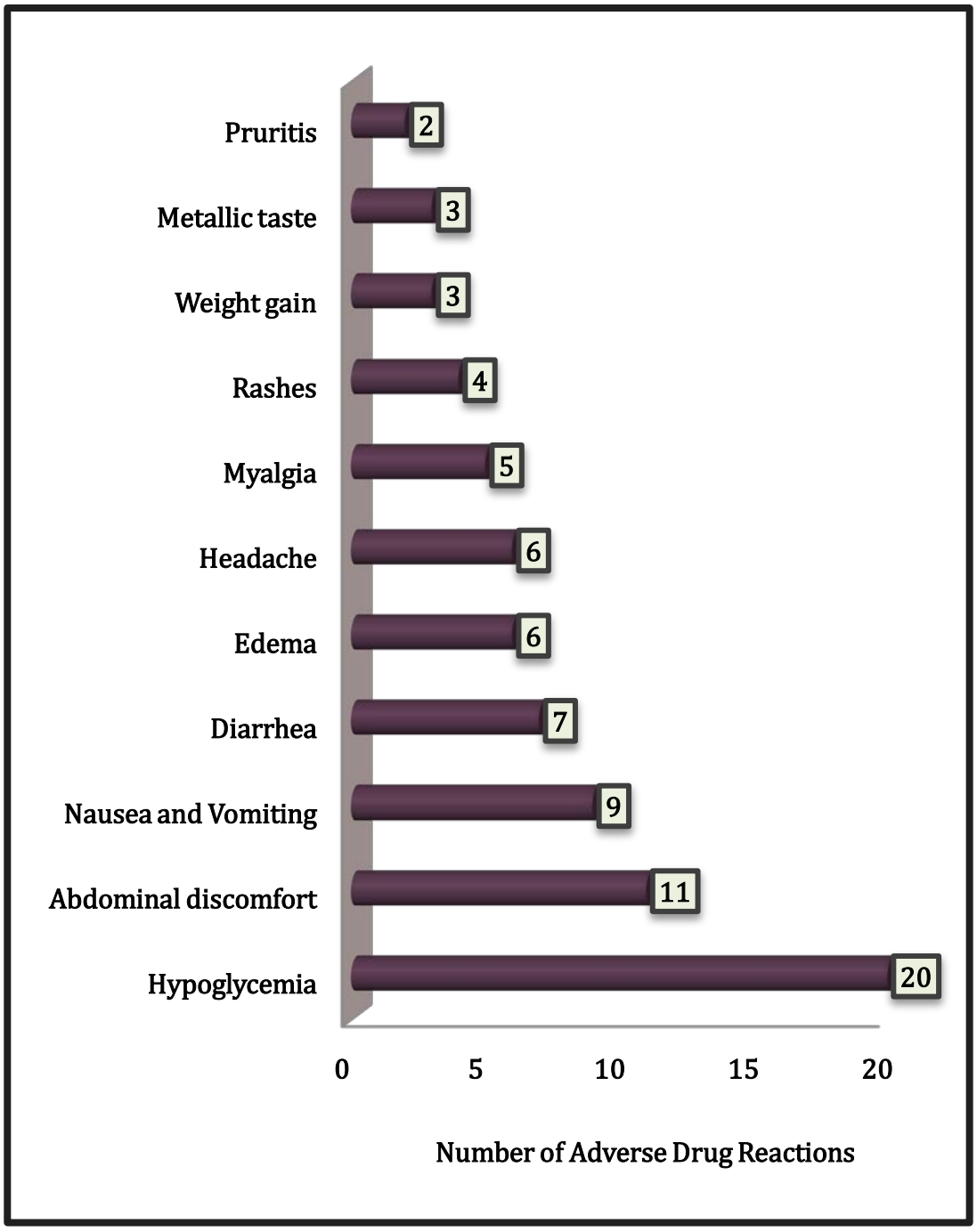


Figure-13: Bar diagram showing ADRs reported by patients due to different classes of antidiabetic drugs as monotherapy

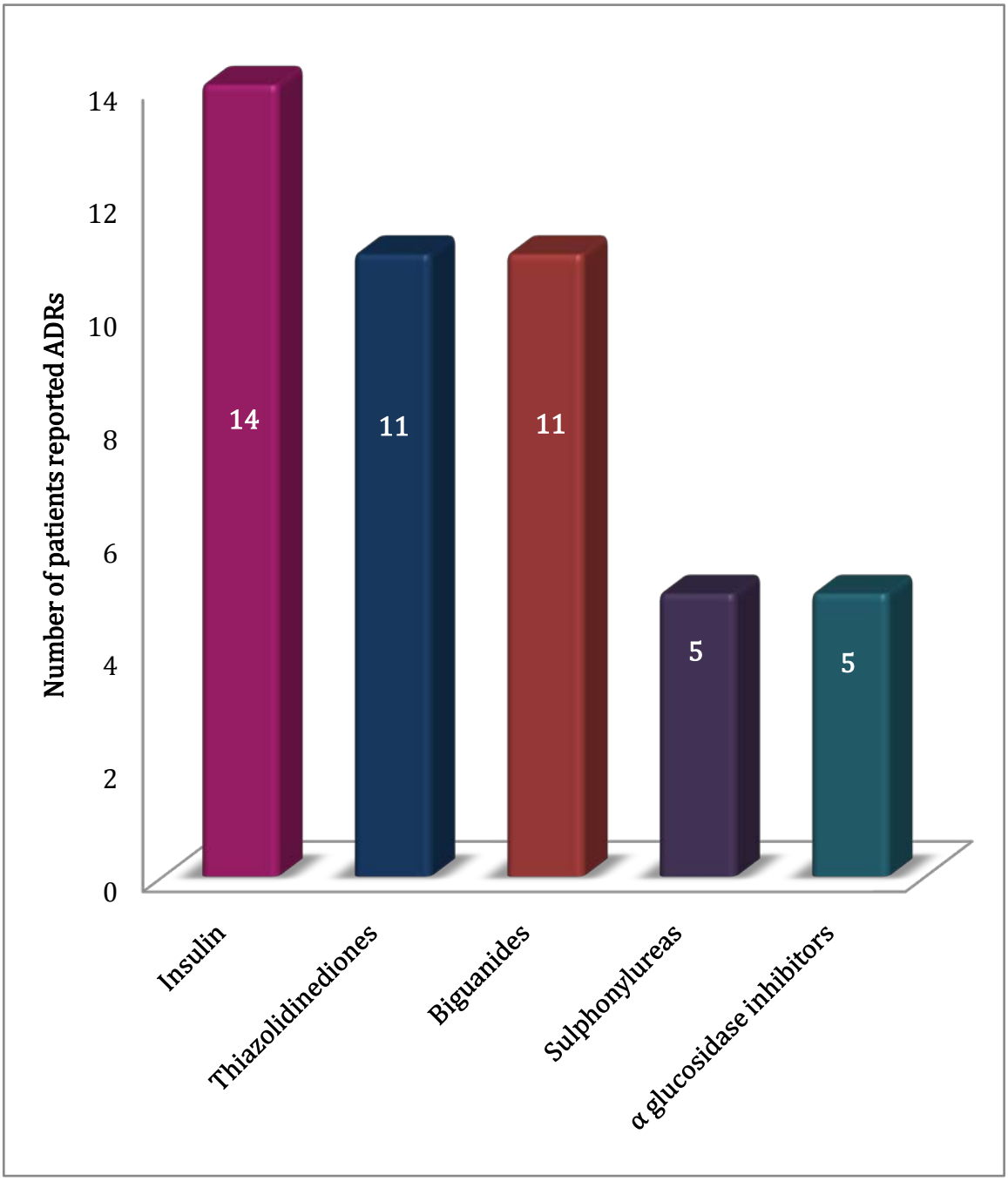


Figure-14: Bar diagram showing number of ADRs reported due to antidiabetic drugs prescribed as combination therapy

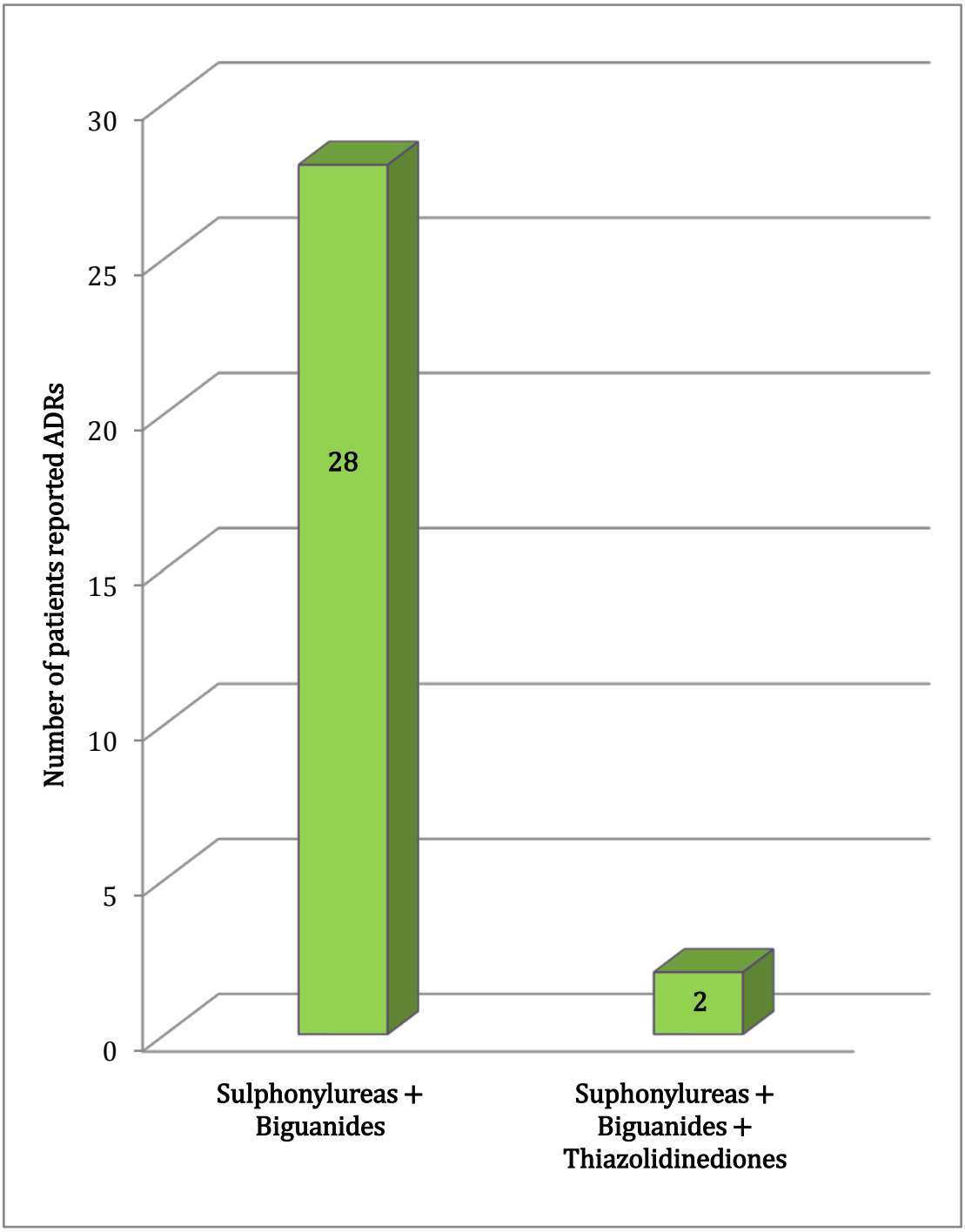
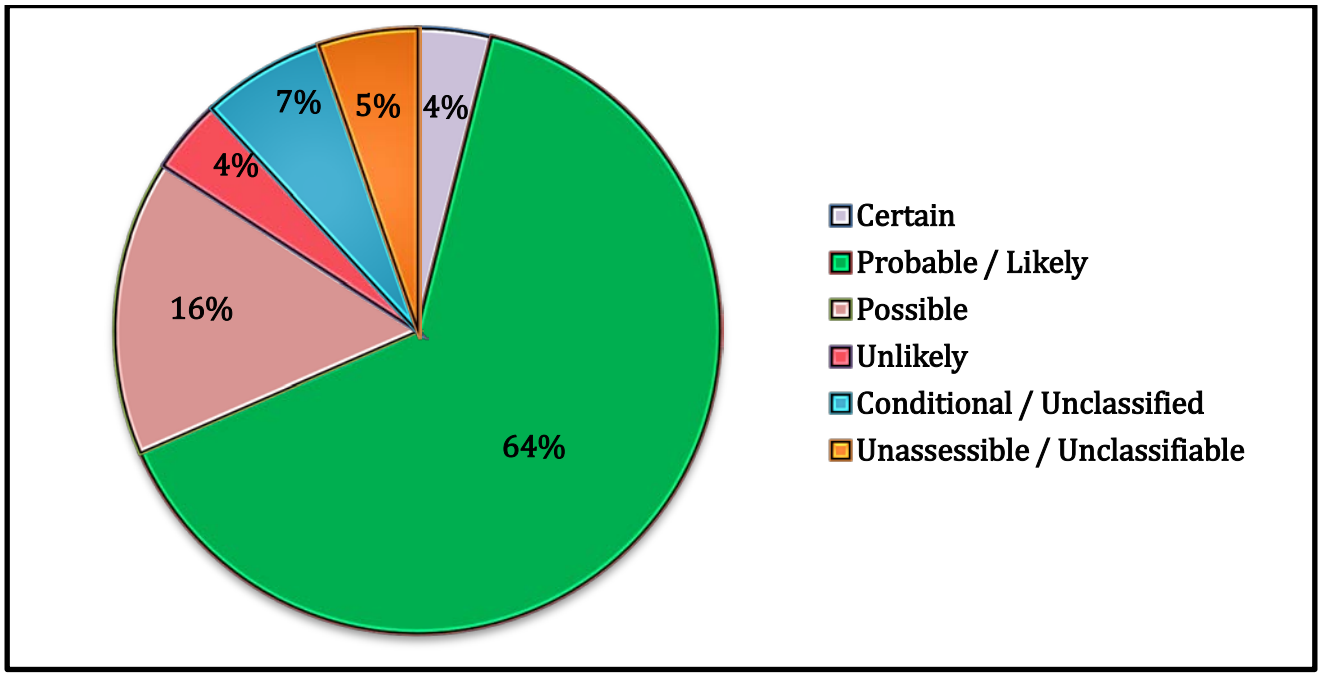


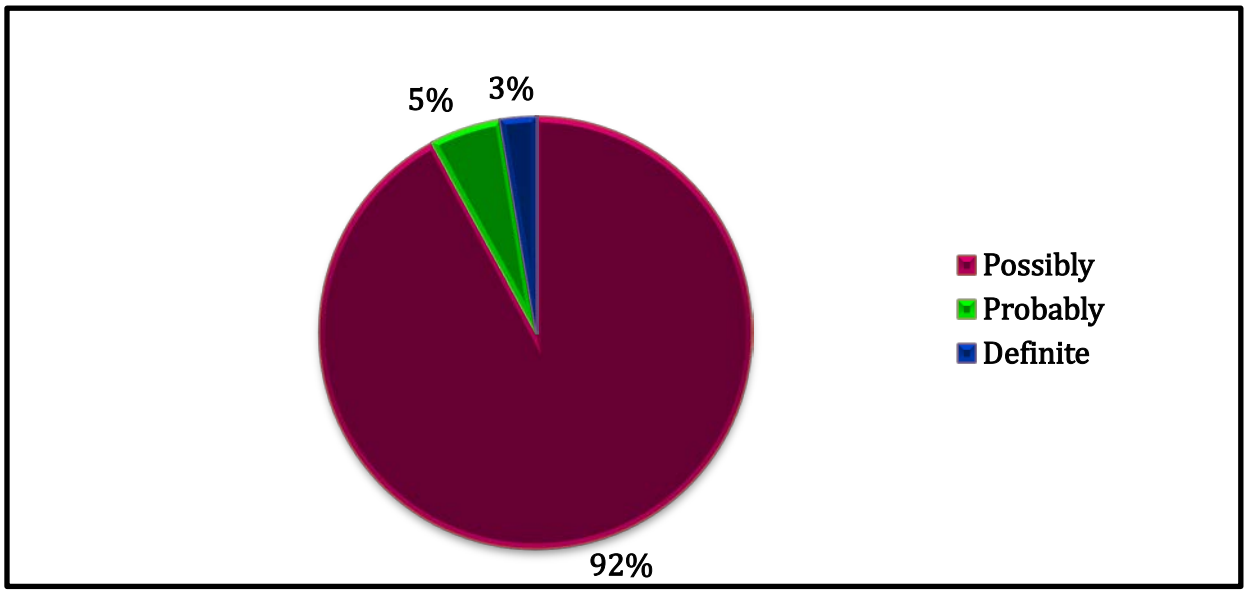
Figure-15: Pie diagram showing the percentage wise distribution of causality assessment of adverse drug reactions due to antidiabetic drugs by WHO scale



WHO scale [101]

Certain	:Clinical event occurring in a plausible time relationship to drug administration, and cannot be explained by concurrent disease or other drugs or chemicals. Response to withdrawal of drug should be clinically plausible. Event must be definitive using a rechallenge procedure.
Probable/Likely	:Clinical event with a reasonable time sequence to administration of drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Possible	:Clinical event, with a reasonable time sequence to administration of drug, which could be explained by concurrent disease or other drugs or chemicals.
Unlikely	:Clinical event occurring with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Conditional/Unclassified	:Clinical event reported as an adverse reaction, about which more data is essential for a proper assessment.
Unassessible/Unclassifiable	:Report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory.

Figure-16: Pie diagram showing the percentage wise distribution of causative relationship of adverse drug reactions due to antidiabetic drugs by Naranjo Scale

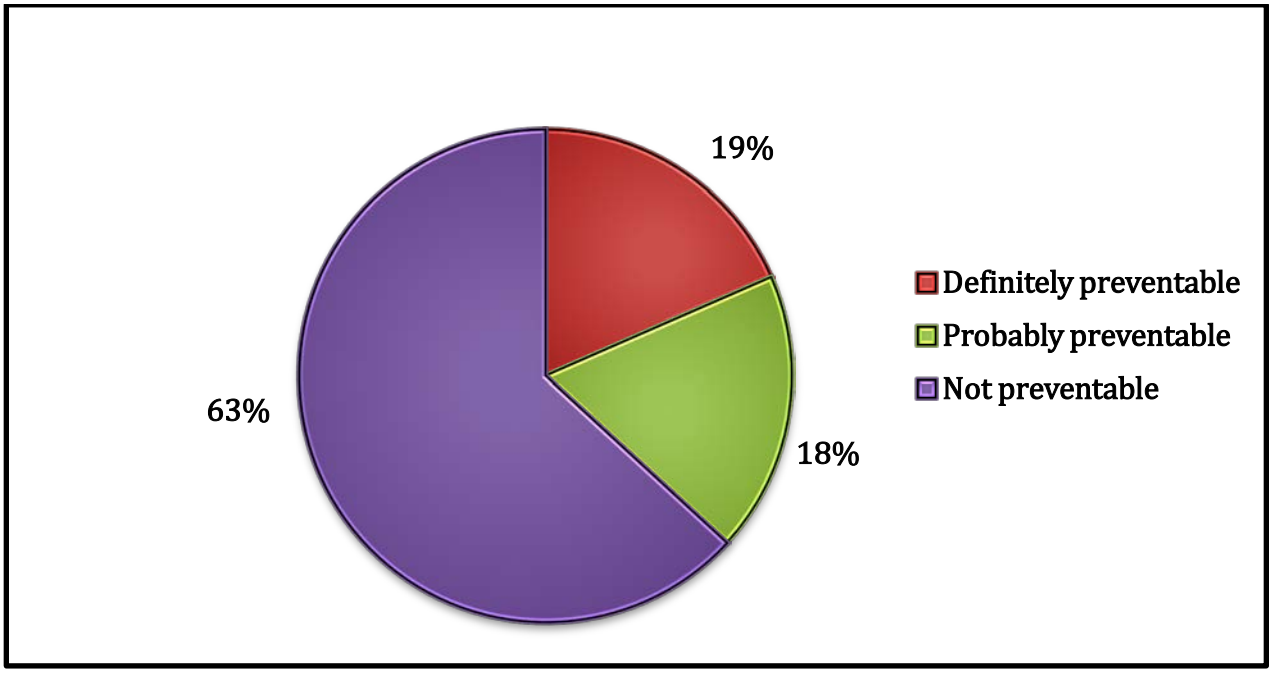


Naranjo Algorithm scale [102]

Total score calculated defines this category as **Possibly (1 to 4), Probably (5 to8) and Definitely (>9)**

Questions	Yes	No	Do not know
Was their previous conclusive report on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered	+2	-1	0
Are their alternative causes (other than the drug) that could have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other body fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the event confirmed by objective evidence?	+1	0	0

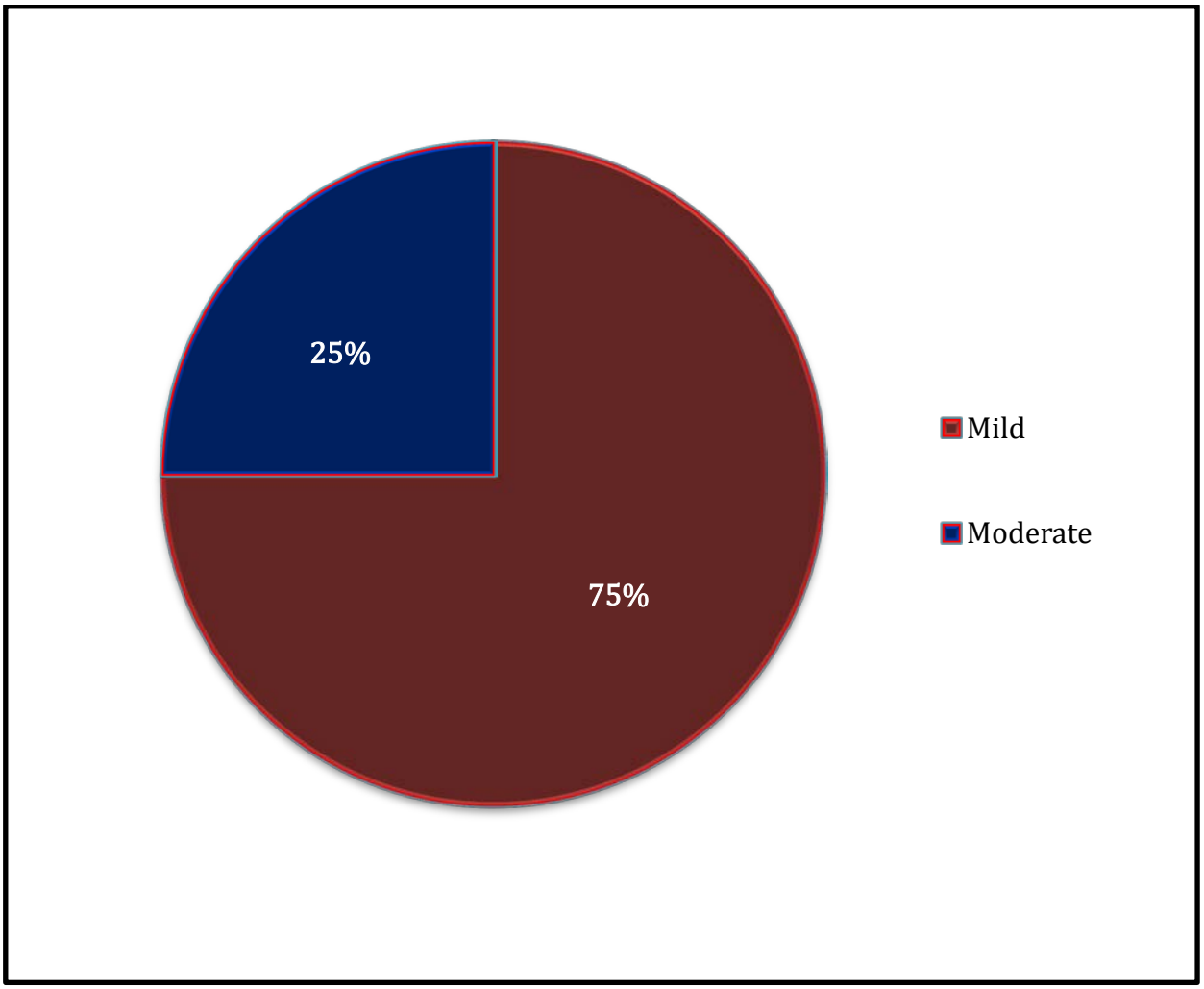
Figure-17: Pie diagram showing the percentage wise distribution of preventability of adverse drug reactions due to antidiabetic drugs by Modified Schumock and Thornton scale



Modified Schumock and Thornton scale [102,103]

i. ii. iii. iv. v.	Was there a history of allergy or previous reactions to the drug? Was the drug involved inappropriate for the patient's clinical condition? Was the dose, route, or frequency of administration inappropriate for the patient's age, weight or disease state? Was a toxic serum drug concentration (or laboratory monitoring test) documented? Was there a known treatment for the adverse drug reaction?	Yes to one or more of the question ADR is **Definitely preventable**
i. ii. iii. iv.	Was required therapeutic drug monitoring or other necessary laboratory tests not performed? Was a drug interaction involved in the ADR? Was poor compliance involved in the ADR? Were preventive measures not prescribed or administered to the patient?	Yes to one or more of the question ADR is **Probably preventable**
	If no to all the above questions	ADR is **Not preventable**

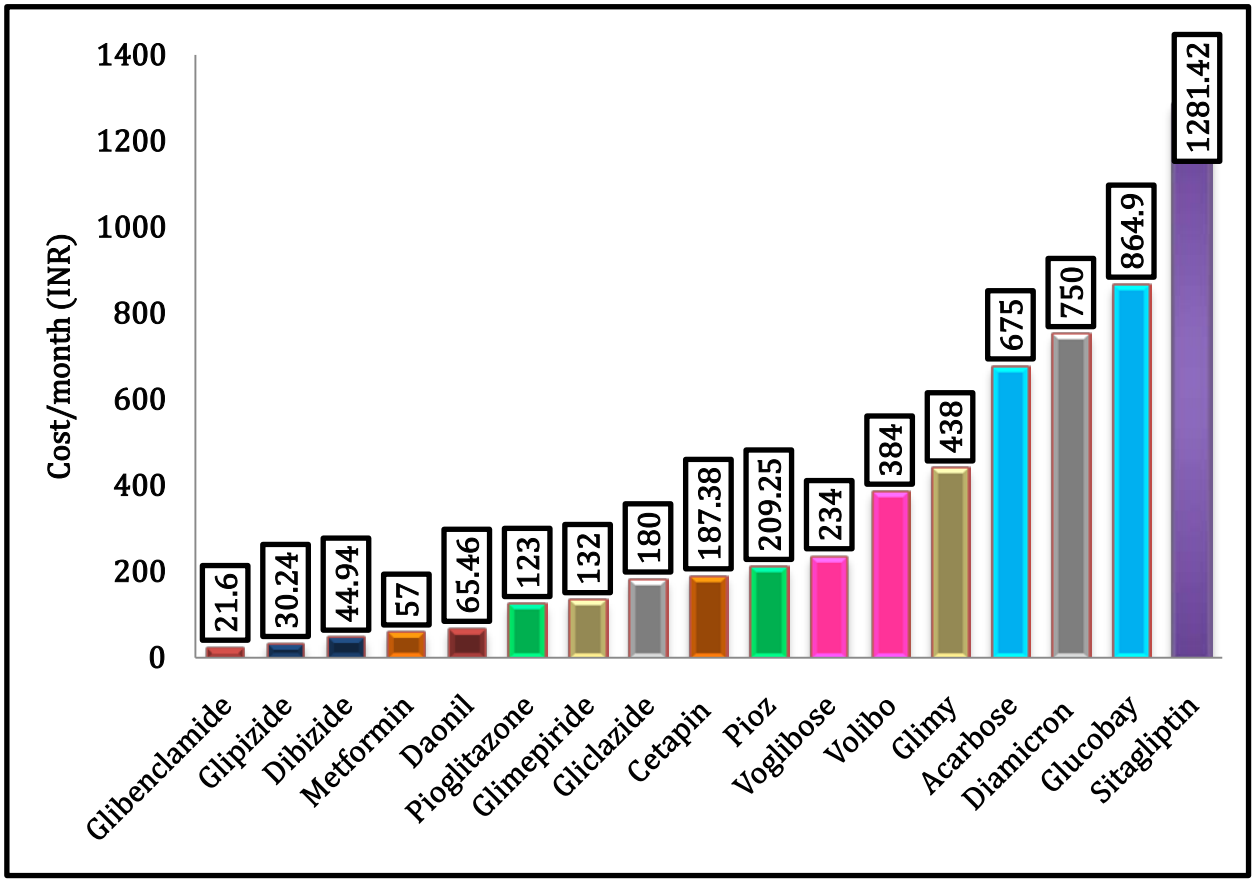
Figure-18: Pie diagram showing the percentage wise distribution of severity of adverse drug reactions due to antidiabetic drugs by Modified Hartwig and Siegel scale



Modified Hartwig and Siegel scale [102,103]

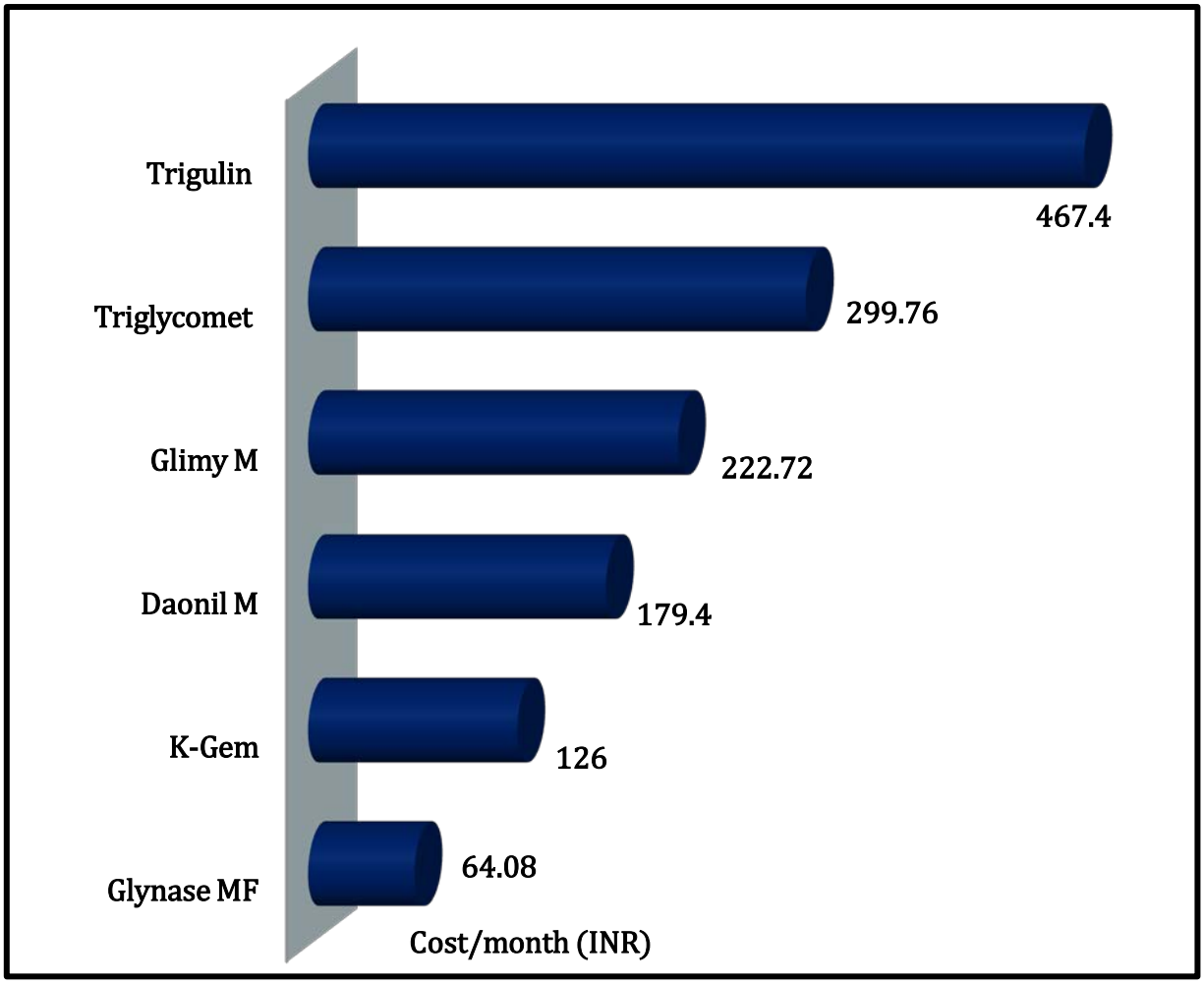
Mild	Level 1:	Require no change in treatment with the suspected drug
	Level 2:	Suspected drug discontinued or changed and no antidote is required
Moderate	Level 3:	Suspected drug discontinued and antidote or other treatment is required
	Level 4(a):	Level 3 that increase length of stay by atleast one day
	Level 4(b):	ADR is the reason for admission
Severe	Level 5:	ADR that requires intensive medical care
	Level 6:	ADR causes permanent harm to patient
	Level 7:	ADR either directly or indirectly leads to death of patient

Figure-19: Bar diagram showing cost of therapy (INR) per month for drugs prescribed as monotherapy



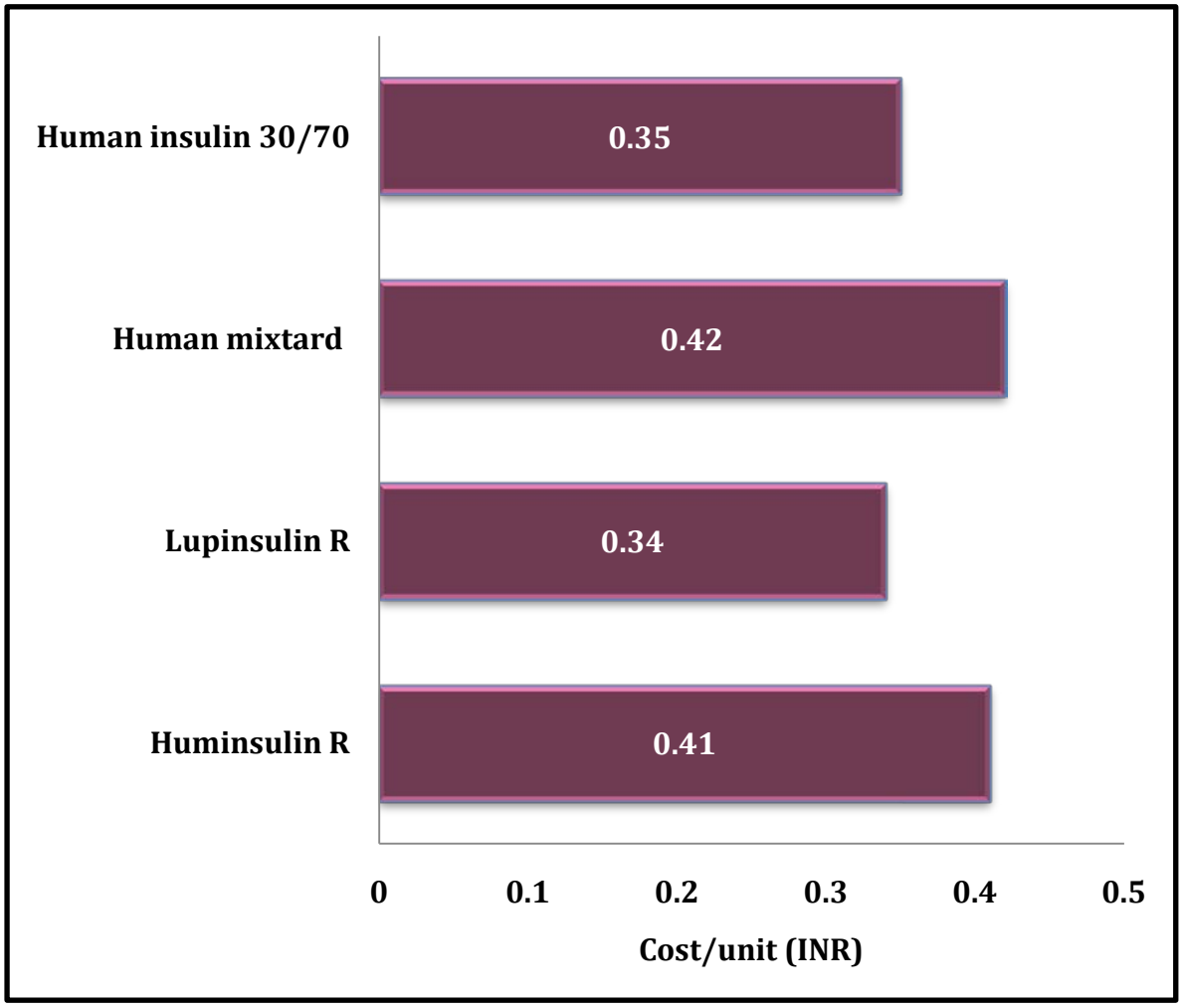
Brand name	Generic name
Dibizide	: Glipizide
Daonil	: Glibenclamide
Cetapin	: Metformin
Pioz	: Pioglitazone
Volibo	: Voglibose
Glimy	: Glimepiride
Diamicron	: Gliclazide
Glucobay	: Acarbose
	Sitagliptin

Figure-20: Bar diagram showing cost of therapy (INR) per month for drugs prescribed as combination therapy



Brand name	Generic name
Glynase MF	: Glipizide + Metformin
K-Gem	: Gliclazide + Metformin
Daonil M	: Glibenclamide + Metformin
Glimy M	: Glimepiride + Metformin
Triglycomet	: Glibenclamide + Metformin + Pioglitazone
Trigulin	: Glimepiride + Metformin + Pioglitazone

Figure-21: Bar diagram showing cost of therapy (INR) per unit of various insulin preparations prescribed



Brand name	Generic name
Huminsulin R	: Regular insulin
Huminsulin 30/70	: Isophane 70% + Soluble 30%
Human mixtard	: Isophane 70% + Biphasic 30%
Lupisulin R	: Regular insulin

Discussion

7. Discussion:

The present study was done to establish the current trend in the prescription pattern and adverse drug reaction profile of antidiabetic drugs in the outpatient department of Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari district. This study has shown the prescription pattern of antidiabetic drugs including rationality in this part of south India. Drug utilization study can improve the quality of treatment by managing this non communicable disease with a cost effective drug prescribed in generic name having tolerable adverse effects. Adverse drug reaction monitoring is still in the developmental stage in India and hence adverse drug reaction monitoring can help the health care professionals to deliver the drug effectively to the community.

This study gave information regarding the frequency of prescription of anti diabetic medication which was higher in women than in men. This is found to be similar to the results obtained from previous studies done by *Kumar et al*.[70]

Obesity and lack of physical activity plays an important role in the development of DM which can further complicate the condition and diminishes the response to treatment. Body mass index in men and women were 28.01 kg/m^2 and 27.82 kg/m^2 respectively. Average BMI of male and female were 37 and 26 respectively in a study conducted by *Akila et al*.[58]

In this study there were no patients diagnosed with type 1 DM and all the patients were either known case or newly diagnosed with type 2 DM. In a study done by *Sutharson et al*.[79] percentage of patients diagnosed with type 2

DM were 98.4%. A study by *Abdi et al*.[104] identified that the percentage of patients with type1 and type 2 DM were 2.28% and 97.71% respectively.

Table No 12: Comparison of results with other studies

Gender	***Kumar et al*.[70]**	**Our study**
Male	48.6%	34.31%
Female	51.4%	65.6%
BMI (kg/m^2)	***Akila et al*.[58]**	**Our study**
Male	37	28.01
Female	26	27.82
Type of DM	***Sutharson et al*.[79]**	**Our study**
Type 1	1.6%	0%
Type 2	98.4%	100%
Clinical presentation	***Akila et al*.[58]**	**Our study**
New	3.15%	13.6%
Known case	96.85%	86.39%
Number of drugs	***Akila et al*.[58]**	**Our study**
Monotherapy	3.15%	27%
Combination therapy	96.85%	73%
Drug of choice	***Shahir et al*.[65]**	**Our study**
Monotherapy	Sulphonylurea 26.74%	Metformin 28.26%
New drugs	***Akila et al*.[58]**	**Our study**
Thiazolidinediones	8.31%	15.21%

BMI: Body mass index

Total of 169 prescriptions were analyzed during the study period out of which 23 (13.6%) were for newly diagnosed while 146 (86.39%) were for known cases of DM. This was comparable with the study conducted by *Akila et al*.[58]

In this study there was a marked decrease in the prescription of drugs by generic name. Drugs prescribed by brand name and generic name were 167 (87%) and 25 (13%) respectively. This observation was similar to the previous study reported by *Acharya et al*.[63]

In our study 73% of the prescriptions were as combination therapy and 27% as monotherapy. There was a decrease in the use of combination therapy compared to the previous study done by *Akila et al*.[58] Metformin was the most frequently prescribed monotherapy in our study. In previous study done by *Shahir et al*.[65] sulphonylurea was the most commonly prescribed class of drug as monotherapy. Switching over to biguanides is a changing trend in the utilization of antidiabetic medication. In our study following biguanides, insulin was used as a single drug to control hyperglycemia. Study done by *Abdi et al* showed a predominant use of parenteral Insulin instead of oral hypoglycemics.[104] In the present study there is a marked increase in the use of thiazolidinediones compared to a study done by *Akila et al*.[58] α-glucosidase inhibitors were also used in few prescription. Utilization of sulphonylurea as monotherapy has decreased while comparing with study done earlier by *Acharya et al*.[63]

In this cross sectional study biguanides was one of the drug utilized in combination therapy. Sulphonylureas were more frequently prescribed along with metformin. Among the sulphonylureas, glimepiride was most commonly

used followed by glipizide. Glibenclamide was the most commonly prescribed sulphonylureas in the year 2003 by *Sutharson et al*.[79] This gradual changeover may be due to decrease in the incidence of hypoglycemic episodes. In our study pioglitazone and voglibose were the newer drugs included in fewer prescriptions. Voglibose has a very good control over post prandial hyperglycemia which is an important contributor in development of microvascular complication.[7]

In this current study, prescriptions containing 3 drug combination therapies were advocated in 10.05% of cases. α-glucosidase inhibitors voglibose, acarbose and DPP-4 inhibitors sitagliptin were the newer drugs prescribed in few patients during the analysis of prescription pattern in our study.

When drug introduced to the heterogenous population following different phases of clinical trial, ADRs not identified earlier may become apparent. Pharmacovigilance plays a vital role in ensuring effective therapy with minimal adverse effects thereby protecting the public.[103]

In the current study hypoglycemia was the most commonly experienced ADR by the diabetic patients. Increased report of hypoglycemia could be due to inappropriate intake of drugs, inappropriate instructions followed or inappropriate intake of food by the patients. Other non pharmacological factors contributing to development of hypoglycemia may be stress and infections.[23] In this study the second most common ADR reported were gastrointestinal disturbances which is again in accordance with the previous study done by *Saravanan et al*.[94]

Assessment of ADRs helps in understanding the relationship of drug and the adverse effect, severity and preventability of the reactions reported. This can gain confidence and improve the adherence to the treatment given.

Our study showed that 64% of the ADRs were probable by using WHO causality assessment scale since the effect developed soon after the administration of drug and not due to concurrent disease or other drugs. 92% of the ADRs scored 1 to 4 by using Naranjo algorithm scale and hence categorised to be possible. Most of the ADRs were not preventable (63%) as per modified Schumock and Thornton preventability scale. Remaining ADRs were either probably or definitely preventable. Hence appropriate dose according to the patient's requirement and appropriate instructions by the treating physician can prevent the ADRs. During the study no serious adverse drug reactions was reported. Most of the ADRs were mild to moderate in degree of severity as per modified Hartwig and Siegel scale.

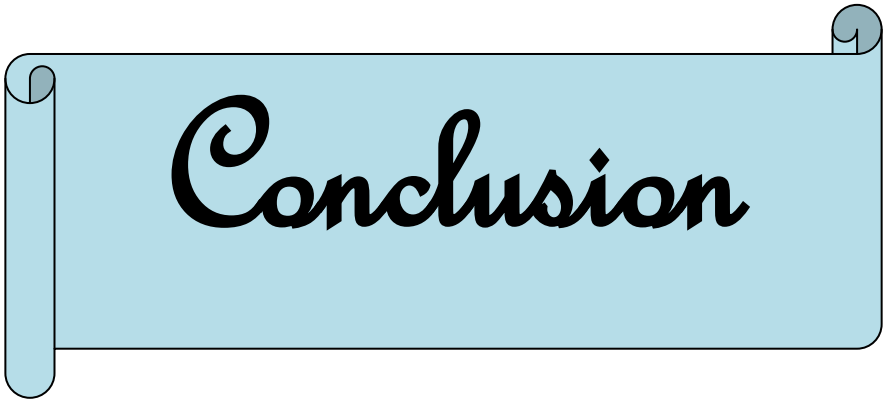
Prescription pattern contribute to the adherence to medication. This is more important in DM since it requires lifelong management. Adherence to the prescribed drug depends on cost effective drug with least adverse effect.[75] The least expensive preparation in our study was metformin and sitagliptin being the most expensive.

While prescribing drugs for other co-morbid conditions, importance must be given while choosing drug. In this study systemic hypertension was the most common co-morbid conditions seen in the diabetic patients. COPD, dyslipidemia, thyroid disorder, cardiovascular disorder, benign prostatic

hypertrophy and depression were the other frequently observed co-morbid conditions.

Rational prescription includes prescribing medication appropriately considering the safety profile and cost effectiveness of the prescribed drug. Appropriate and effective monitoring of ADR is the best way to safeguard the public. In a country like India with varied socioeconomic status, it is important to have a vigilant Pharmacovigilance programme. Management of DM rationally can improve adherence to therapy, minimise adverse effects and prolong the time for development of microvascular and macrovascular complication thereby effectively reducing the morbidity and mortality.

Limitations of our study were socioeconomic state of the diabetic patients was not analyzed and glycemic control was not assessed. The availability of drugs in the hospital and the intake by the patients in the various age groups would have been a better method of DUS.


Conclusion

8. Conclusion:

In cross sectional study conducted during the period of August 2013 to August 2014 to evaluate the drug utilization pattern of antidiabetic drugs found that the 73% of drugs prescriptions were by monotherapy and 23% by combination therapy and all were found to be rational. The study also showed that the 86.98% of prescriptions were by brand names and rest were by generic names. The pharmacoeconomics of the antidiabetic drugs prescribed in the study revealed that glibenclamide was the least expensive and sitagliptin as the most expensive drugs prescribed as monotherapy and in the combination therapy the least expensive was glipizide with metformin and most expensive was the combinations of glimepiride, metformin and pioglitazone.

In this study the ADRs were found probable (64%), possible (16%), conditional (7%), unclassifiable (5%), certain (4%) and unlikely (4%) by using WHO causality assessment scale. By using Naranjo algorithm scale it was found that ADRs were possible in 92%, probable in 5% and definite in 3% of cases. Modified Schumock and Thornton scale for preventability of ADRs showed that ADRs were not preventable in 63%, definitely preventable in 19% and probably preventable in 18% of cases. Modified Hartwig and Siegel scale for severity of ADRs showed that 75% of the ADRs reported were mild and rest were moderate. This study also found that combination of sulphonylureas with biguanides was responsible for most of the ADRs and among all the ADRs reported hypoglycemia was the commonest followed by pruritis as the least common.


Summary

9. Summary:

DM is a metabolic disorder with disastrous effect on major organ system if not treated appropriately. Drug utilization studies are designed to evaluate the use of different classes of drugs in a population both quantitatively and qualitatively. DM is an endocrine disorder which needs lifelong therapy. Adverse effect and pharmacoeconomics of drugs have a major impact on adherence to therapy.

Hence this cross sectional study was done to study the prescription pattern, adverse effects and pharmacoeconomics of drugs used in the treatment of DM. 169 prescriptions were analyzed during the study period. Our study revealed that antidiabetic most frequently utilized was metformin which was in accordance with the guidelines.[34] Utilization of newer drugs shows the importance of prescribing antidiabetic medication based on evidence based medicine among the treating physician. DM was treated frequently with combination of metformin and glimepiride.

Adverse effect most commonly encountered during the study period was hypoglycemia. Majority of the ADRs were due to combination of antidiabetics. Majority of the reported ADRs were probable using WHO scale and possible using Naranjo scale. Most of the ADRs were not preventable as per modified Schumock and Thornton scale. It was concluded that all the ADRs were not severe as assessed by modified Hartwig and Siegel scale.

Pharmacoeconomic evaluation showed a dramatic increase in the cost of monotherapy when prescribed using brand names compared to generic name of drugs.

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10. References:

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Annexure

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161

Phone No: 04651-280866. Fax No. 04651-280740

Institutional Human Ethics Committee

Ref. No. SMIMS/IHEC/2013/A/21 **Date: 1st July 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/A/21,** entitled "A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Anti Diabetic Drugs in Patients Attending SMIMS" submitted by Dr. Shanthi M, Postgraduate of Department of Pharmacology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 30th of May 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

SMIMS INSTITUTE OF MEDICAL SCIENCES
IHEC
Date. 03/07/2013

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam (K.K District)
Tamil Nadu -629161

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

KULASEKHARAM, Kanyakumari District Tamilnadu-629161

Institutional Human Ethics Committee [IHEC]

Date: 07th May 2014

Dr. Shanthi M, Postgraduate student, Department of Pharmacology of this Institution had applied for change in title (Letter dated 05/05/2014) for the study entitled "A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antidiabetic Drugs in Patients Attending SMIMS." This is required as per the regulations of the Tamil Nadu Dr. M.G.R Medical University where the name of the institute should not be used in the title of the study. Hence the candidate is permitted to change the title as **"A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antidiabetic Drugs in Patients Attending A Teaching Hospital."** This is to carry out the study in the approved period given by the IHEC.

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES * KULASEKHARAM * IHEC Date..07/05/2014

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
SMIMS, Kulasekharam [K. K District]
Tamilnadu -629161

CONSENT FORM

PART 1OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

Dear Volunteers,

We welcome you and thank you for your keen interest in participation in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. **Name of the Principal Investigator**	:	**Dr.Shanthi.M** Post Graduate (I yr) Department of Pharmacology SMIMS, Kulasekharam
2. Name of the Guide	:	**Dr. Rema Menon. N** Professor and Head Department of Pharmacology SMIMS, Kulasekharam
3. Name of the Co-Guide	:	(i) **Dr. Kaniraj Peter. J** Professor and Head Department of Medicine SMIMS, Kulasekharam (ii) **Dr. Madhavrao. C** Assistant Professor Department of Pharmacology SMIMS, Kulasekharam

4. Institute: Sree Mookambika Institute of Medical Sciences, Kulasekharam-629161, Kanyakumari district, Tamilnadu

5. Title of the study: A study of drug utilization pattern and adverse drug reaction profile of antidiabetic drugs in patients attending a teaching hospital

6. Background information: Prevalence of Diabetes mellitus is progressing rapidly worldwide. Fourth leading cause of death is due to this non-communicable disease. Response to anti-diabetic drugs varies in different population. Drug utilization research establishes the current trend in the use of anti-diabetic drugs and adverse drug reaction including the new drug and to identify irrational prescription. Irrational prescription can affect the adherence to drugs thereby not reaching therapeutic goal ultimately rising the economic burden. Since you are diagnosed to be diabetic and on treatment with anti diabetic drugs it is proposed to do the study to evaluate the drug utilization-pattern and adverse drug reactions of anti-diabetic drugs in the Medicine out-patient department of this institution.

7. Aims and objectives: To, assess the following in the outpatient department (OPD) of Medicine, Sree Mookambika Institute of Medical Sciences Kulasekharam (K.Kdistrict.TN)

i. The pattern of anti diabetic drugs prescription

ii. Rationality of using anti diabetic drugs as mono therapy and combination therapy

iii. The prescription writing pattern by brand name and generic name

iv. The pharmacoeconomic of anti diabetic drugs prescribed for one month

v. To study adverse drug reaction profile of anti diabetic drugs prescribed

8. Scientific justification of the study: Drug utilization research establish current trend in the use of anti diabetic drugs and adverse drug reactions including the new drug and to identify irrational prescription. Irrational prescription can affect the adherence to drugs thereby not reaching therapeutic goal ultimately rising the economic burden. Till date no study on drug utilization pattern and adverse drug reaction profile of anti diabetic drugs is conducted in this institution. Hence it has been proposed to conduct the study to evaluate the drug utilization pattern

and adverse drug reaction profile of anti diabetic drugs in the Medicine outpatient department of this institution.

9. Procedure for the study: The study will be carried out after getting informed written consent from each participant. The study will not have any impact on the treatment given by physician. Study will be carried out in collaboration with the Medicine department. Enrolled subject name, age, sex, co-morbid condition and treatment if any will be recorded in a predesigned case record form. Details of the prescribed anti diabetic drug(s) will be recorded. Conclusion of the study will be made from the details in the case record form.

10. Expected risks for the participants: This study does not involve any risk to the participant

11. Expected benefits of research for the participants: This study does not provide any direct benefit to the participant, however the data obtained from the study will be useful for better medical health care in the future

12. Maintenance of confidentiality: Will be maintained

13. Why have I been chosen to be in this study? You are diagnosed as diabetes mellitus (Type1/Type2) and prescribed with anti diabetic drugs, hence according to the inclusion and exclusion criteria you are recruited into this study.

14. How many people will be in the study? 157

15. Agreement of Compensation to the participants (In case of a study related injury): Not applicable

16. Anticipated prorated payment, if any, to the participant(s) of the study: No

17. Can I withdraw from the study at any time during the study period?

The study participant can withdraw from the study at any time and will not involve any penalty or loss of benefits to which the participant is otherwise entitled.

18. If there is any new findings / information, would I be informed? Yes

19. Expected duration of the Participant's participation in the study: 1 day

20. Any other pertinent information: No

21. Whom do I contact for further information?

For any study related queries, you are free to contact

Dr.Shanthi.M
Post Graduate
Department of Pharmacology
SMIMS
Mobile number: 9442406103
Email:dr_shanthisenthil@yahoo.com

Place: Kulasekharam

Date :

Signature of the Principal Investigator

Signature of the Participant

CONSENT FORM

PART 2 OF 2

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled **'A study of drug utilization pattern and adverse drug reaction profile of antidiabetic drugs in patients attending SMIMS'**

Serial no/Reference no:

Name of the Participant:

Address of the Participant:

Signature of the participant

Witnesses:

1.

2.

Date:

Place: Kulasekharam

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

KULASEKHARAM

Department of Pharmacology

Title of study: A Study of Drug Utilization Pattern and Adverse Drug Reaction Profile of Antidiabetic drugs in patients attending a teaching hospital

Case Record Form

Serial No: Medicine OPD Reference No:

Participant Name: Age: Sex:

Address: Ht: Wt:

Diagnosis :

Sl.No	Formulation	Drug name (as prescribed by the physician)	Dose	Frequency	Duration	ROA*	Before or after food	Generic name	Cost (Rs)/mth

* Route of administration

Associated co-morbid condition(s):

Concurrent drugs taken for other co-morbid conditions:

Adverse drug reactions reported by participants:

(If adverse reaction experienced details will be filled up in CDSCO ADR form)

Adverse drug reaction	Experienced/Not experienced
Hypoglycaemia	
Nausea, Vomiting	
Jaundice	
Anaemia	
Hypersensitivity reaction	
Weight gain	
Edema	
Resistance	
Lipoatrophy, Lipohypertrophy	
Any other ADRs	

Place: Kulasekharam

Date: **Signature of the Principal Investigator**

Abbreviations

ADA	:American Diabetes Association
ADR	:Adverse drug reaction
AIIMS	:All India institute of medical sciences
AMPK	:Adenosine 5' monophosphate activated protein kinase
BMI	:Body mass index
BPH	:Benign prostatic hypertrophy
CDA	:Canadian Diabetes Association
CDSCO	:Central drugs standard control organization
COPD	:Chronic obstructive pulmonary disease
CSII	:Continuous subcutaneous insulin infusion
DM	:Diabetes mellitus
DPP-4	:Dipeptidyl peptidase 4 inhibitors
DUR	:Drug utilization research
DUS	:Drug utilization study
ESRD	:End stage renal disease
FBPase	:Fructose 1,6 bisphosphatase
GIP	:Glucose dependent insulinotropic polypeptide
GLP-1	:Glucagon like polypeptide 1
GLUT	:Glucose transporter
GSK-3	:Glycogen synthase kinase 3
HbA1C	:Glycosylated haemoglobin
HLA	:Human leucocyte antigen
HNF	:Hepatocyte nuclear transcription factor
IAP	:Islet amyloid peptide
IgE	:Immunoglobulin E

IHEC	:Institutional Human Ethics Committee
INR	:Indian rupee
IPF	:Insulin promoter factor
IRS	:Insulin receptor substrate
K_{ATP}	:Adenosine 5' triphosphate sensitive potassium channel
MODY	:Maturity onset diabetes of young
MDI	:Multiple dose insulin
NPH	:Neutral protamine Hagedorn
OHA	:Oral hypoglycemic agent
OPD	:Out-patient department
PCOS	:Polycystic ovarian syndrome
PDRM	:Preventable drug related morbidity
PPAR	:Peroxisome proliferator activated receptor
PPRE	:Peroxisome proliferator activated receptor response element
PvPI	:Pharmacovigilance programme of India
RXR	:Retinoid X receptor
SGLT-2	:Sodium glucose co-transport 2
SUR	:Sulphonylurea receptor
TNF α	:Tumour necrosis factor α
UMC	:Uppsala monitoring centre
WHO	:World health organisation