



## International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR | Volume 10 | Issue 4 | Oct - Dec - 2022  
www.ijamscr.com

ISSN:2347-6567

Review article

Medical research

### A review article on different types of medications used in diabetes mellitus

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#### ABSTRACT

To achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Achieving near-normal glycated hemoglobin significantly, decreases risk of macrovascular and microvascular complications. At present there are different treatments, both oral and injectable, available for the treatment of type 2 diabetes mellitus (T2DM). Treatment algorithms designed to reduce the development or progression of the complications of diabetes emphasizes the need for good glycaemic control. The aim of this review is to perform an update on the benefits and limitations of different drugs, both current and future, for the treatment of T2DM. Initial intervention should focus on lifestyle changes. Moreover, changes in lifestyle have proven to be beneficial, but for many patients is a complication keep long term. Physicians should be familiar with the different types of existing drugs for the treatment of diabetes and select the most effective, safe and better tolerated by patients. Metformin remains the first choice of treatment for most patients.

**Keywords:** Type 2 diabetes mellitus, Treatment, Oral antidiabetic agents, Injectable antidiabetic agents, Older people, Renal impairment, Future treatments etc.

#### INTRODUCTION

Diabetes mellitus is a term for several conditions Involving how body turns food into energy. When A person eat carbohydrate and it turns out as glucose. This glucose molecule send into the blood stream. In body the pancreas release a hormone which is called insulin and the function is send the glucose molecules from the blood stream to the cells. If the pancreas do not release insulin sufficiently it can cause build up of glucose in bloodstream yeah but which is the condition called hyperglycemia or high blood sugar.(1) There is no cure for diabetes. with the treatment and lifestyle changes The patient can leave a long and a healthy life.

#### TYPES OF DIABETES

There are three types of diabetes

**Pre diabetes:** Pre diabetes is The blood sugar is higher than

It should be but not high to diagnose as diabetes.

**Type-1 diabetes:** it is an autoimmune disease. It happens when immune system attack pancreas.

**Type-2 diabetes:** Insulin dependent diabetes is type-2 diabetes As it begins in the childhood it is also called as juvenile onset diabetes. It happens when the organ fail to produce insulin Specifically pancreas.

**Gestational diabetes:** This occurs in the stage of pregnancy Unconscious some form of insulin resistance. There are several drugs in treating diabetes. Many drugs are coming up with their beneficial effects according to the patient condition Focusing on the patient compliance and underlining diseases, So various types of drugs used currently to treat diabetes are listed in detail.

#### Oral anti-diabetic drugs

A. The drugs which Enhance insulin secretion:

## 1.SULFONYL UREAS

### A.TOLBUTAMIDE

It is a first generation potassium channel blocker, sulfonyl urea oral hypoglycemic medication. It is used to management of type2 DM. It stimulates of insulin by the pancreas. (2)

**MECHANISM OF ACTION:** It lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body use insulin for this drug to work.

**SIDE EFFECTS:** hypoglycemia, weight gain, hypersensitivity, cardiovascular risk, renal or liver disease.

**DRUG INTERACTIONS:** Increased hypoglycemia with cimetidine, insulin, salicylates and sulfonamides.

### 2.GLIMEPIRIDE

It is also used to treat of type2 DM. It lowers blood sugar by causing the pancreas to produce insulin.

**COMPLICATIONS:** Heart disease, stroke, kidney problems, nerve damage and eye problems.

**SIDE EFFECTS:** Dizziness, nausea, yellowish of the skin or eyes, light coloured stools, dark urine, unusual bleeding, diarrhoea, fever.

**GLIMEPIRIDE THE SAME AS METFORMIN:** Metformin improves the insulin resistance, and is administered as the first choice medication for type2 DM. Glimepiride is a third generation of sulfonyl urea that stimulates insulin secretion.(3)

**GLIMEPIRIDE BETTER THAN METFORMIN:** Glimepiride is an effective drug for lowering blood sugar, but it can cause weight gain. Metformin is first choice of drug to control blood sugar and lower the risk of death from DM.

**MECHANISM OF ACTION:** Bind to the sulfonyl urea receptor on the surface of the beta cell and closes KATP channels to inhibit potassium efflux presence of depolarizing the beta cells and increase insulin secretion.

**GLIBENCLAMIDE:** It is an oral hypoglycemic drug that stimulates the pancreatic beta cells to secrete insulin. It is used to treat to DM and DM during pregnancy.

**SIDE EFFECTS:** hypoglycemia, nausea, heart burn, vomiting, diarrhoea, abdominal pain, weight pain.

**GLIPIZIDE:** It is used to treat high blood sugar levels caused by type2 DM. Glipizide and metformin are not the same because Glipizide is a sulfonyl urea that treats type2 DM in adults. In children are 10 years of age, Glipizide and metformin work in different ways and dosages.(4)

**SIDE EFFECTS:** nausea, vomiting, loss of appetite, diarrhoea, constipation, upset stomach, headache, weight gain.

## 3.MEGLITININ OR PHENYLALANINE ANALOGUES

**A.REPAGLINIDE:** It is used to treat of type2 in adults to adjust to diet and exercise and sometimes with other drugs like metformin

**SIDE EFFECTS:** Back, leg pains, loosening of the skin, darkened urine, body swelling, tiredness and weakness, indigestion, itching

**MECHANISM OF ACTION:** Binds to receptors on pancreatic beta cells and stimulates insulin release. It is a short acting drug.

**B.NATEGLINIDE:** It is also meglitinide used to treat non insulin of DM. It belongs to the class of short acting insulin.

**SIDE EFFECTS:** headache, nasal congestion, runny nose, joint aches, back pain, constipation, cough.

## 4.DIPEPTIDYL PEPTIDASE -4(DPP-4) INHIBITORS

**A .SITAGLIPTIN:** It is used to treat of type2 DM

**MECHANISM OF ACTION:** Increased insulin production and decreased hepatic glucose overproduction.

**SIDE EFFECTS:** feeling hungry, shaking, sweating, confusion, difficulty concentrating.

**B.VILDAGLIPTIN:** It is used to treat to control blood sugar levels with type2 DM **SIDE EFFECTS:** headache, dizziness, hypoglycemia, nausea, weight gain, tremors.

**MECHANISM OF ACTION:** Binds covalently to the catalytic site of DPP-4, eliciting prolonged enzyme inhibition.

**A.Overcome insulin resistance:**

1.Biguanides (AMPK Activators) Eg: metformin

2. Thiazolidinediones (PPAR $\gamma$  activator) Eg: Pioglitazone

**BIGUANIDES:** (Eg: METFORMIN)

Biguanides do not cause insulin release but the insulin presence is important for these action. These medications reduces glucose which is produced by the liver. It also improves how insulin works in body and reduce the conversion of carbohydrates into glucose in the body.(5)

**Mechanism of action:** Metformin increases hepatic adenosine monophosphate activated protein kinase activity, thus reducing hepatic gluconeogenesis and lipogenesis increasing insulin mediated uptake of glucose in muscles.

Metformin causes activation AMPK leading to Interferences with mitochondrial respiratory chain and promotes glucose utilization. Retards absorption of glucose, hexose, amino acids, vit B12.

**Administration of metformin:** It is the initial drug of choice in type 2 diabetes mellitus. It is given orally in 500 – 1000mg tablets with a full glass of water twice a day.

**Adverse effects**

- GI upset such as diarrhea (12-53%)
- Nausea and vomiting (7-26%)
- Flatulence ( 4-12%)
- Chest discomfort
- Flushing
- Palpitations
- Headache ( 5-6%)
- Chills and dizziness
- Diaphoresis
- Vit B12 deficiency
- In less than 1% patients it causes lactic acidosis and it is precipitated by conditions predisposing to hypoperfusion and hypoxemia such as severe renal failure.

**Contraindications**

- Hypersensitivity to the drug
- Heart failure
- Hepatic and respiratory diseases
- Alcoholics
- Severe renal dysfunction ( eGFR less than 30ml/min)
- Metabolic acidosis including diabetic ketoacidosis

### Monitoring

The patients who are taking metformin ,initial and frequent monitoring of hemoglobin ,RBC indices and renal functional tests before therapy initiation and atleast every year. The

clinician should repeat these tests for every 3 – 6 months if GFR is 45 to <60ml/min. Serum vitB12 and folate levels should be tested if the patient taking metformin for long time to detect megaloblastic anemia condition.(6)

**THIAZOLIDINEDIONES:** (Eg: pioglitazone, rosiglitazone)

These medications improve the way insulin works by allowing more glucose entry into muscles, fat and the liver.

**Mechanism of action:**

It is a selective agonist for the nuclear peroxisome Proliferated activated receptor  $\gamma$  (PPAR $\gamma$ ) expressed mainly in fat cells, and in muscle cells. It increases insulin sensitivity And resultant peripheral uptake of glucose can occurs. It enhances insulin responsive genes transcription and tendsto reverse insulin resistance by GLUT4 receptor expression.(7) This PPAR $\gamma$  can increases the level of adiponectin (fat tissue secreted cytokine) can increases not only the no. of insulin sensitive adipocytes but also stimulates fatty acid oxidation. Supresses hepatic gluconeogenesis: Additionally, these medications lowers the sr. triglycerides and raises HDL cholesterol.

**Administration of thiazolidinediones:** Pioglitazone is given as 15mg, 30mg, and 45mg tablets through oral route daily. Rosiglitazone is given as 2mg, 4mg and 8mg daily but it is rarely used medication.

### Adverse effects

- Edema (less than or equal to 27%)
- Hypoglycemia (less than or equal to 27%)
- Cardiac failure (less than or equal to 8%)
- Bone fracture (less than or equal to 5%)
- Myalgia (5%)
- Sinusitis (6%)
- Pharyngitis
- Headache and weight gain
- Plasma volume expansion
- Mild anemia
- Contraindications :
- Hypersensitivity
- CHF
- Serious hepatic impairment
- Bladder cancer
- History of macroscopic haematuria
- In pregnancy

### Miscellaneous drugs

#### 1. Alpha glucose inhibitors Mechanism of action

It works by breaking down the carbohydrates into tiny sugar molecules like glucose. These work by competitive and reversible inhibition of intestinal enzymes and slow down the digestion of carbohydrates and option delays the glucose absorption. They can be taken with insulin or other oral anti diabetic drugs in it is used to treat diabetes in combination with exercise and diet.(8)

**Side effects:**

- Palpitations
- Swelling of lips
- Constipation is the severe side effect
- Unusual bleeding
- Diarrhea that may be watery or bloody

- Liver problems
- Nausea
- stomach pain

**Administration:**

The dose of the drug for the individual patient is based on the efficacy of the drug and the tolerability of a person. The dosing should be bell checked and prescribed by the physician. some of the initial doses of few drugs in this category are listed below

Miglitol Voglibose

Acarbose: initial dose 25mg PO TID

Maintenance dose 50-100mg PO TID

Maximums dose 50 mg PO TID (above 60 kgs 100mg PO TID)

#### 2. Amylin analogues

**Mechanism of action:** Amylin analogs inhibit Glucagon secretion there by delays the gastric emptying and suppress the food intake. It is a polypeptide hormone. It is secreted in the beta cells of the pancreas. Amylin and insulin decrease in diabetes and as amylin is used in glucose control, these drugs are used in treating diabetes. Pramlintide man-made hormone and present naturally in the body It works by three mechanisms.

1. It slows the rate of the food from stomachs to intestine
2. Lowers the glucose production from liver
3. Control appetite and leads to less food intake

**Sides -effects:**

- Nausea
- Severe hypoglycemia
- Loss of appetite
- weight loss
- Vision problem
- Weakness
- Sweating
- Headache
- Tachycardia

**Administration:**

These drugs are to be taken subcutaneously Before major meals. Pramlintide: usual adult dose 15mcg SC (type-1 DM). Adult dose 60mcg SC (type-2 DM).

#### 3. SGLT-2 inhibitors

These are also called as sodium glucose cotransporter 2 inhibitors and gliflozins.

**Mechanism of action**

They act on the SGLT 2 proteins located in the kidneys and thereby prevent the reabsorption of glucose back into the blood Resulting in excretion of more glucose in the urine. These agents are used in decreasing the levels of glucose as well as also used in weight loss and with the beneficial effect of lower risk to hypoglycemia. These also have specific action of independently acting on beta cells of pancreas.(9)

**Eg:** Dapagliflozin

It works on the SGLT 2 which is located in the proximal tubule of the nephron and thereby increasing the excretion of the glucose from the body and acting as antidiabetic agent

**Administration :**

Dapagliflozin: initial dose 5-10mg PO OD (based on estimates GFR)

**Side effects:**

#### Ketoacidosis

- Female genital mycotic infection

- Nasopharyngitis
- Increased urination
- Dyslipidemia
- Constipation
- Pain in extremity
- Influenza
- Arthralgia

#### 4. Dopamine D2 agonists

**Mechanism of action** These agents are used to treat type 2 diabetes. These drugs act by two mechanisms by reducing the glucose production by the liver and improving how the body uses insulin. They act by binding to proteins called dopamine receptors.

**Bromocriptine**

It is the medicine which gives quick relief and was approved by FDA. Bromocriptine is proved to reset abnormally elevated hypothalamic drive for Enhanced plasma glucose, free fatty acids, and triglycerides in insulin resistant patients.

**Administration :**

Bromocriptine: adult dose 0.8mg OD taken within two hours after waking up in the morning Maximum dose: 4.8mg/ day

**Side effect :**

- Nausea
- Constipation
- Stomach cramps
- Heart burn
- Depression
- Difficulty in sleeping
- Bloody vomit
- Seizures
- Hallucinations
- Blurred vision
- Numbness
- Water discharged from the nose

**Injectable Medications to Treat Diabetes**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are injectable medications to treat type 2 diabetes and obesity. GLP-1 agonist Also known as GLP-1 receptor agonist, incretin mimetics or GLP-1 analogues. (10)

These drugs are used in a similar manner to insulin as subcutaneous injections mostly used jointly with Other drugs used to treat diabetes mellitus. Based on difference in dosing schedule and duration of action there are various GLP-1 RAs. Some among them are listed

- exenatide (Byetta)
- dulaglutide (Trulicity)
- semaglutide (Ozempic, Wegovy)
- liraglutide (Saxenda, Victoza)
- lixisenatide (Adlyxin)
- pramlintide (Symlinpen)
- tirzepatide (Mounjaro)

Patients who are contraindicated or intolerance to metformin should be treated along with GLP-1 analogues Also used in patients with haemoglobin A1c Greater than 1.5% over target also in patients who do not reach the target A1c In three months specifically in patients suffering with atherosclerosis, heart failure, or chronic kidney disease.

Obesity is also treated with GLP-1 analogue Liraglutide in higher dose according to FDA it is used in overweight patients

with comorbidities.

**Categories:**

Human GLP-1 backbone Dulaglutide

Albiglutide Liraglutide Semaglutide Exenatide-4 backbone Eventide Lixisenatide

**Mechanism of Action:**

Glucagon-like peptide-1 and glucose dependent insulinotropic polypeptide (GIP) both incretin hormones inactivated by dipeptidylpeptidase-4 (DPP-4) this stimulates Insulin secretion after an oral glucose load via the incretin effect. This processor is not seen or absent in type 2 DM.

The pharmacological benefits of this therapy is, it delays the gastric emptying and also inhibits the production of Glucagon from pancreatic alpha cells when the blood sugar levels are high. These drugs also show affect in decreasing pancreatic beta cell apoptosis while promotes their proliferation.

**Other benefit:**

In addition to treat diabetes these drugs also have other beneficial effects on the following conditions

- Obesity
- weight loss
- lowering both systolic and diastolic blood pressure
- decrease in total cholesterol
- improve left ventricular ejection fraction
- Improve myocardial contractility
- coronary blood flow
- Improve cardiac output
- improve cardiac output
- Improve endothelial function while reducing in fraction size
- Increase glucose uptake in the muscle
- decrease glucose production in the liver
- Neuroprotection
- Increase satiety due to direct action on hypothalamus

**Administration:**

As GLP-1 Has poor bio availability when given orally these are administered subcutaneous. Summary of dosing frequencies for some commonly prescribed drugs are given below.

Exenatide is only drug which should be administered twice a day remaining drugs are administered only once.

Dulaglutide - once weekly Albiglutide - once weekly

Liraglutide - once daily Exenatide BID - twice daily

Exenatide QW - once weekly Lixisenatide - once daily.

**Adverse effects:**

**Side effects on using GLP include**

- Nausea
- Vomiting
- Diarrhoea Which may lead to acute kidney injury
- Dizziness
- Tachycardia
- Infections
- Dyspepsia and headaches.
- Contraindications
- Pregnancy
- Severe renal impairment
- Severe gastrointestinal diseases

Pramlintide is another drug which can be Injected in patients

with diabetes and it is used in conjunction with mealtime insulin shots. This is less preferably used in treating patients but it works in similar manner to GLP-1 RAs.

Mechanism of action:

It's an injectable amylin analogue. This drug has primarily 3 mechanism of actions slowing the gastric emptying suppressing in appropriate postmeal Glucagon secretion increasing satiety.

Administration: This injection should be given under the skin of stomach or upper thigh and this should not be injected along with insulin or should not be injected in the same site of insulin administration. The dosing of the insulin should also be adjusted while initiating this injection. It is recommended to be administered before each meal that includes at least 250 calories or 30 grams of carbohydrates.

adverse effects:

- Redness, swelling,
- itching at the site of injection
- Loss of appetite
- Dizziness

- Cough
- Joint pain
- sore throat

## CONCLUSION

As diabetes being the major disorder worldwide it should be treated effective manner together with patient counselling as it plays an important roll in improving overall health of a patient. Detailed information of the medication including the mechanism of action and dosage adjustment for the patient based on the demographics and underlying diseases of the patient is important and the social status of the patient including risk factors along with the family history are helpful in effective patient counselling and therapy some outing for the better medication adherence in treating diabetes. Various kinds of drugs and drugs used as injections and oral drugs are given in detail which provide you the basic information for administration of the drug in treating diabetes.

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