

## Antidiabetic Drugs

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### Oral Agents:

They are useful for type 2 DM that cannot be managed by diet alone.

Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents.

**Notes:** long-standing DM may require a combination of oral agents with or without insulin.

Oral glucose-lowering agents include:

- (1) Insulin secretagogues
- (2) Insulin sensitizers
- (3)  $\alpha$ - Glucosidase inhibitors
- (4) Dipeptidyl peptidase-IV inhibitors
- (5) Sodium–glucose cotransporter 2 inhibitors
- (6) Others.

#### 1. Insulin secretagogues

##### (Sulfonylureas & Glinides)

They promote insulin release from pancreas, so their action depend on functioning pancreatic  $\beta$  cells.

##### A. Sulfonylureas (SUs)

Include the 1<sup>st</sup> generation (**Tolbutamide**) & 2<sup>nd</sup> generation drugs (**Glyburide** "**Glibenclamide**", **Glipizide** & **Glimepiride**).

##### MOA:

- 1) Block ATP-sensitive  $K^+$  channels, resulting in depolarization &  $Ca^{2+}$  influx, & insulin exocytosis.
- 2) Reduce hepatic production of glucose & increase peripheral sensitivity to insulin.

##### kinetics:

- Bind to serum proteins, excreted in the urine and feces.
- Duration of action is the shortest for **tolbutamide** (6-12 hours), while that of 2<sup>nd</sup> generation is ranged from 12 to 24 hours.

##### Adverse effects:

- Weight gain, hyperinsulinemia & hypoglycemia.
- Used with caution in patients with hepatic or renal insufficiency.
- **Glyburide** is metabolized to active compounds, thus glipizide or glimepiride are safer options in renal dysfunction and in elderly.
- **Glyburide** has minimal transfer across the placenta, and it may be an alternative to insulin for DM during pregnancy.

##### ORAL AGENTS

Acarbose **PRECOSE**  
Glimepiride **AMARYL**  
Glipizide **GLUCOTROL**  
Glyburide **DIA\_ETA**,  
**GLYNASE PRESTAB**  
Metformin **FORTAMET**,  
**GLUCOPHAGE**  
Miglitol **GLYSET**  
Nateglinide **STARLIX**  
Pioglitazone **ACTOS**  
Repaglinide **PRANDIN**  
Rosiglitazone **AVANDIA**  
Saxagliptin **ONGLYZA**  
Sitagliptin **JANUVIA**  
Tolbutamide  
**TOLBUTAMIDE**  
Canagliflozin **INVOKANA**  
Bromocriptine **CYCLOSET**  
Colesevelam **WELCHOL**  
Dapagliflozin **FARXIGA**

**Drug interaction:**

- 1- Atypical antipsychotic, Corticosteroids, Diuretics, Niacin, Phenothiazines & Sympathomimetics reduce **SUs** effects.
- 2- Azole antifungals, Beta-blockers, Chloramphenicol, Clarithromycin, Monoamine oxidase inhibitors, Probenecid, Salicylates & Sulfonamides potentiate **SUs** effects.

**B. Glinides****Repaglinide & Nateglinide.****MOA:**

- Bind to a distinct site on the **SUs** receptor of ATP-sensitive potassium channels.
- In contrast to **SUs**, glinides have a rapid onset & a short duration of action.

Effective in the early release of insulin occurs after a meal & are categorized as postprandial glucose regulators. Glinides should be taken prior to a meal.

- glinides should not be used in combination with **SUs** due to overlapping mechanisms of action which increase the risk of serious hypoglycemia.

**Adverse effects:**

- Incidence of hypoglycemia & weight gain is lower than that with **SUs**.
- **Repaglinide** effect may be enhanced by ketoconazole, itraconazole, fluconazole, erythromycin & clarithromycin, whereas decreased by barbiturates, carbamazepine & rifampin.
- Concurrent use of **repaglinide** with **gemfibrozil** (lipid-lowering drug) is contraindicated because the later inhibits hepatic metabolism resulting in severe hypoglycemia.
- Used cautiously in patients with hepatic impairment.

**2. Insulin sensitizers (Biguanides & Thiazolidinediones)**

They improve target-cell response to insulin without increasing insulin secretion.

**A. Biguanides: Metformin**

- The only currently available biguanide.
- It increases glucose uptake & use by target tissues, decreasing IR.

**MOA:**

1. Main mechanism is reduction of hepatic gluconeogenesis (**Note:** In type 2 DM excess glucose produced by the liver is a major source of hyperglycemia, accounting for fasting hyperglycemia).
  2. Slows intestinal absorption of sugars, improving peripheral glucose uptake & utilization.
- Weight loss due to appetite loss.
  - The ADA recommends **metformin** as the initial drug of choice for type 2 DM.
  - Used alone or in combination with other oral agent or insulin.

- Hypoglycemia may occur when **metformin** is taken with insulin or insulin secretagogues (dose adjustment may be required).

**kinetics:** Not bound to serum proteins and not metabolized.

#### **Adverse effects:**

- Largely are gastrointestinal.
- **Metformin** is contraindicated in presence of renal dysfunction due to the risk of lactic acidosis.
- It should be discontinued in cases of acute MI, exacerbation of HF, sepsis, or other disorders that can cause acute renal failure.
- Used cautiously in old patients (< 80 years) & in those with a history of HF or alcohol abuse.
- Should be temporarily discontinued in patients undergoing diagnosis requiring IV radiographic contrast agents.
- Rarely, potentially fatal lactic acidosis has occurred.
- Long-term use may interfere with vitamin B12 absorption.

#### **Other uses:**

Treatment of polycystic ovary syndrome (PCOS). It lowers IR in women with PCOS that can result in ovulation and, possibly pregnancy.

#### **B. Thiazolidinediones (TZDs) (glitazones)**

- No risk of hyperinsulinemia.
- Include glitazones pioglitazone & Rosiglitazone.

#### **MOA:**

- Act as agonists on peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ), a nuclear hormone receptor, thus, increase sensitivity to insulin in adipose tissue, liver & skeletal muscle.
- Hyperglycemia, hyperinsulinemia, hypertriglyceridemia & elevated HbA1c levels all are improved.
- **Rosiglitazone** increases LDL cholesterol & triglycerides, whereas **pioglitazone** decreases triglycerides.
- Both drugs increase HDL levels.
- **TZDs** are used as monotherapy or in combination with other oral agents or insulin (insulin dose should be lowered).
- **Pioglitazone** is recommended as a 2<sup>nd</sup> or 3<sup>rd</sup> line alternative for patients who fail or have contraindications to **metformin** therapy.
- **Rosiglitazone** is not recommended because of the cardiac adverse effects.

**kinetics:**

- Some metabolites of **pioglitazone** have activity.
- The majority of the active **pioglitazone** & its metabolites are excreted in the bile, whereas **rosiglitazone** metabolites are primarily excreted in the urine.
- No dose adjustment is required in renal impairment.
- **TZDs** should be avoided in nursing mothers.

**Adverse effects:**

- Liver function monitoring is recommended because liver toxicity was reported with the use of these drugs.
- Weight gain possibly because TZDs may increase SC fat & cause fluid retention (can worsen HF), thus TZDs should be avoided in patients with severe HF.
- Osteopenia & increased fracture risk may occur with TZDs use.
- **Pioglitazone** may increase bladder CA risk.
- Risk of MI & death from CV causes restrict **rosiglitazone** use.
- After a further review of safety data, the restrictions on **rosiglitazone** use were subsequently lifted.

**Other uses:** PCOS.

**3.  $\alpha$ - Glucosidase inhibitors : Acarbose & Miglitol****MOA:**

- They reversibly inhibit  $\alpha$ -glucosidase enzymes (in the intestinal brush border), if these drugs taken at the start of a meal they delay carbohydrates break down into glucose & other simple sugars, thus lowering postprandial glucose levels.
- **Acarbose** also inhibits pancreatic  $\alpha$ -amylase, thereby interfere with the breakdown of starch to oligosaccharides.
- Do not cause hypoglycemia, but their combination with insulin secretagogues or insulin, may cause hypoglycemia which should be treated with glucose rather than sucrose ( because sucrase is also inhibited).

**kinetics:**

- **Acarbose** is poorly absorbed, metabolized by intestinal bacteria & some of its metabolites are absorbed & excreted in the urine.
- **Miglitol** is very well absorbed but has no systemic effects, excreted unchanged by the kidney.

**Adverse effects:**

- Flatulence, diarrhea & abdominal cramping.
- Should not be used in the presence of inflammatory bowel disease, colonic ulceration, or intestinal obstruction.

**4. Dipeptidyl peptidase - IV (DPP-4) inhibitors:****Alogliptin, Linagliptin, Saxagliptin & Sitagliptin**

**MOA:** Inhibit DPP-4 enzyme preventing the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1), increasing insulin release in response to meals & reduce inappropriate secretion of glucagon.

- Used as monotherapy or combined with SU, metformin, TZDs or insulin.
- Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral.

**kinetics:**

- All DPP-4 inhibitors except **linagliptin** (eliminated via the enterohepatic system) require dosage adjustments in renal dysfunction (note: **alogliptin** and **sitagliptin** are excreted unchanged, whereas **saxagliptin** is metabolized into an active metabolite).

**Adverse effects:**

- Nasopharyngitis, headache & pancreatitis.
- Ritonavir, atazanavir, itraconazole, and clarithromycin, may inhibit **saxagliptin** metabolism.

**5. Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors: Canagliflozin & Dapagliflozin****MOA:**

- Inhibit SGLT2 (which reabsorbs filtered glucose in the kidney), decreasing glucose reabsorption & increasing its excretion.
- Also sodium reabsorption is decreased resulting in osmotic diuresis, that may reduce systolic BP, though, SGLT2 inhibitors are not indicated for HT treatment.

**kinetics:**

- Given once daily in the morning, **canagliflozin** should be taken before the first meal of the day.
- Both drugs are metabolized to inactive metabolites.
- **Canagliflozin** is primarily excreted via the feces, & about one-third of a dose is renally eliminated.
- These agents should be avoided in patients with renal dysfunction.

**Adverse effects:**

- Genital mycotic infections in female (e.g., vulvovaginal candidiasis), UTIs, and urinary frequency.
  - Hypotension, occurred, in elderly or patients on diuretics (evaluate volume status before treatment).
- 6. Other agents: Bromocriptine and colesevelam** (bile acid sequestrant) cause modest reductions in HbA1c by unknown mechanism.
- Their clinical use for treatment of type 2 DM is limited by their modest efficacy, adverse effects, and pill burden.