Oral hypoglycemic agents:

They include: (1) Insulin secretagogues (2) Insulin sensitizers (3) α-Glucosidase inhibitors (4) Dipeptidyl peptidase - IV inhibitors.

1. Insulin secretagogues

Useful for:

- Type 2 diabetes that cannot be managed by diet alone.
- Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are those most likely to respond well to oral glucose-lowering agents.
- Patients with long-standing disease may require a combination of glucose-lowering drugs with or without insulin to control their hyperglycemia.

Notes:

1. Insulin is added because of the progressive decline in β cells that occur due to the disease or aging.
2. Oral glucose-lowering agents should not be given to patients with type1 diabetes

A. Sulfonylureas (SUs)

Classified as insulin secretagogues, because they promote insulin release from the pancreas. The primary drugs used today are the 1st generation (**tolbutamide**) & the 2nd generation drugs (**"glyburide " glibenclamide, glipizide** & **glimepiride**).

Mechanism of action:

1) Stimulate insulin release from the β cells of the pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization & Ca2+ influx.

2) Reduce hepatic production of glucose

3) Increase peripheral sensitivity to insulin.

Pharmacokinetics and fate:

- Bind to serum proteins, metabolized by the liver, and excreted by the liver or kidney.
- Duration of action is the shortest for Tolbtamide (6-12 hours), while that of 2nd generation is ranged from 12 to 24 hours.

Adverse effects:

- Weight gain, hyperinsulinemia & hypoglycemia.
- Used with caution in patients with hepatic or renal insufficiency.
- Renal impairment is a particular problem with the use of agents that are metabolized to active compounds such as **glyburide.**
- **Glyburide** may be a safe alternative to insulin therapy during pregnancy because it has minimal transfer across the placenta.

Drug interaction:

1- Phenylbutazone, Salicylates & Sulfonamides displace SUs from plasma proteins.

2- Allopurinol, Probenecid, Salicylates & Sulfonamides decrease urinary excretion of SUs or their metabolism.

3- Dicuramol, Chloramphenicol, MOIs, Phenylbutazone, reduce hepatic metabolism of SUs.

B. Glinides (Meglitinides)

They include **Repaglinide** & **Nateglinide**.

Although they are not SUs, they have common actions.

Mechanism of action:

- Their action is dependent on functioning pancreatic β cells.
- 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 that occurs after a meal & are categorized as postprandial glucose regulators.
- Combined therapy of these agents with **metformin** or the glitazones has been shown to be better than monotherapy with either agent.
- Glinides should not be used in combination with SUs due to overlapping mechanisms of action.

Pharmacokinetics and fate:

- Well absorbed orally after being taken 1 to 30 minutes before meals.
- Metabolized to inactive products by cytochrome P450 in the liver & are excreted through the bile.

Adverse effects:

- Hypoglycemia is lower than that with SUs.
- **Repaglinide** effect may be enhanced by **ketoconazole**, **itraconazole**, **fluconazole**, **erythromycin** & **clarithromycin**, whereas opposed by other drugs, such as **barbiturates**, **carbamazepine** & **rifampin**.
- **Repaglinide** causes severe hypoglycemia when taken concomitantly with **gemfibrozil** (lipid-lowering drug) & concurrent use is contraindicated.
- Weight gain is less than with the SUs.
- Used cautiously in patients with hepatic impairment.

2. **Insulin sensitizers**

- Two classes **Biguanides** & **Thiazolidinediones**.
- They improve target-cell response to insulin without increasing pancreatic insulin secretion.

A. Biguanides: Metformin

- The only currently available biguanide.
- It increases glucose uptake & use by target tissues, thereby decreasing insulin resistance.
- The risk of hypoglycemia is far less than that with SUs. .
- Hypoglycemia may only occur if caloric intake is not adequate or exercise is not compensated for calorically.

Mechanism of action:

1. Main mechanism is the reduction of hepatic glucose output, largely by inhibiting hepatic gluconeogenesis.

Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for the high blood glucose on waking in the morning.

2. Slows intestinal absorption of sugars & improves peripheral glucose uptake & utilization.
3. An important property of this drug is its ability to modestly reduce hyperlipidemia (LDL & VLDL cholesterol concentrations fall & HDL cholesterol rises).

- These effects may not be apparent until 4 - 6 weeks of use.
- weight loss because of appetite loss.
- Recommended as the drug of choice for newly diagnosed type 2 diabetics.
- **Metformin** may be used alone or in combination with one of the other agents as well as with insulin.
- Hypoglycemia may occur when **metformin** is taken with insulin (dose of insulin may require adjustment because **metformin** decreases the hepatic production of glucose).

Pharmacokinetics and fate:

- Well absorbed orally, is not bound to serum proteins and not metabolized.
- Excretion is via the urine.

Adverse effects:

- Largely are gastrointestinal.
- **Metformin** is contraindicated in presence of renal and/or hepatic disease and diabetic ketoacidosis.

- It should be discontinued in cases of acute MI, exacerbation of CHF & severe infection.
- Used cautiously in patients older than age 80 years & in those with a history of CHF or alcohol abuse (**note**: diabetics being treated with HF medications should not be given **metformin** because of an increased risk of lactic acidosis).
- 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:

Effective in the treatment of polycystic ovary disease. Its ability to lower insulin resistance in these women can result in ovulation and, therefore, possibly pregnancy.

B. Thiazolidinediones (TZDs) (glitazones)

- Hyperinsulinemia wih these agents is not a risk.
- **Troglitazone** was the first TZD but was withdrawn (deaths due to hepatotoxicity).
- The two members of this class currently available are **pioglitazone** & **rosiglitazone**.

Mechanism of action:

- They are known to target the peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear hormone receptor.
- Ligands for PPARγ regulate adipocyte production & secretion of fatty acids as well as glucose metabolism, resulting in increased insulin sensitivity in adipose tissue, liver & skeletal muscle.
- Hyperglycemia, hyperinsulinemia, hypertriglyceridemia & elevated HbA1c levels are improved.
- LDL level is not affected by **pioglitazone**, whereas it is increased by **rosiglitazone**.
- Both drugs increase HDL levels.
- **Pioglitazone** & **rosiglitazone** can be used as monotherapy or in combination with other glucose-lowering agents or insulin (insulin dose should be lowered).
- **Pioglitazone** is recommends as a 2nd -line alternative for patients who fail or have contraindications to **metformin** therapy.
- **Rosiglitazone** is not recommended due to concerns regarding cardiac adverse effects.

Pharmacokinetics and fate:

- Both **pioglitazone** & **rosiglitazone** are well absorbed after oral administration & are extensively bound to serum albumin.
- Both undergo extensive metabolism by different CYP450 isozymes.
- Some metabolites of **pioglitazone** have activity.
- Renal elimination of **pioglitazone** is negligible, with the majority of the active drug & metabolites excreted in the bile & eliminated in the feces.
- The metabolites of rosiglitazone are primarily excreted in the urine.
- No dose adjustment is required in renal impairment.
- Their use is not recommended in nursing mothers.

Adverse effects:

- Due to deaths from hepatotoxicity in patients who take troglitazone, it is recommended that liver enzyme levels of patients on these medications be measured initially and periodically thereafter.
- Very few cases of liver toxicity have been reported with rosiglitazone or pioglitazone.
- Weight increase can occur, possibly because TZDs may increase SC fat or cause fluid retention(can lead to or worsen heart failure).
- TZDs have been associated with osteopenia & increased fracture risk.
- Risk of MI & death from CV causes with rosiglitazone has been identified.
- Other adverse effects of the TZDs include headache & anemia.
- TZDs reduce plasma concentration of the estrogen-containing contraceptives & pregnancy may occur.

Other uses:

Relief of insulin resistance with the TZDs can cause ovulation in premenopausal women with polycystic ovary syndrome.

3. α- Glucosidase inhibitors

Acarbose & miglitol

Orally active drugs used for the treatment of type 2 diabetes.

Mechanism of action

- Taken at the beginning of meals.
- Act by delaying the digestion of carbohydrates, thereby resulting in lower postprandial glucose levels.
- They reversibly inhibit membrane-bound α- glucosidase in the intestinal brush border (an enzyme responsible for the hydrolysis of oligosaccharides to glucose & other sugars).

- **Acarbose** also inhibits pancreatic α- amylase, thereby interfering with the breakdown of starch to oligosaccharides.
- Consequently, the postprandial rise of blood glucose is blunted.
- They neither stimulate insulin release nor increase insulin action in target tissues. Thus, as monotherapy, they do not cause hypoglycemia.
- However, when used in combination with the SUs or with insulin, hypoglycemia may develop (**note**: hypoglycemia should be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs).

Pharmacokinetics and fate

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

Adverse effects

- The major side effects are flatulence, diarrhea & abdominal cramping.
- These drugs should not be used in the presence of inflammatory bowel disease, colonic ulceration, or intestinal obstruction.

4. Dipeptidyl peptidase - IV inhibitors

Sitagliptin

- Orally active dipeptidyl peptidase-IV (DPP-IV) inhibitors used for the treatment of patients with type 2 diabetes.

Mechanism of action

- Inhibits the enzyme DPP-IV, thus prevents the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1).
- Incretin hormones in turn, increase insulin release in response to meals & reduce inappropriate secretion of glucagon.
- DPP-IV inhibitors may be used as monotherapy or in combination with a SU, **metformin**, glitazones or insulin.

Pharmacokinetics and fate

- Well absorbed after oral administration, food do not affect the absorption.
- Majority of **sitagliptin** is excreted unchanged in the urine.
- Renal dysfunction necessity dose adjustments.

Adverse effects

- Well tolerated, with the most common adverse effects being nasopharyngitis & headache.
- As monotherapy or in combination with **metformin** or **pioglitazone**, the rates of hypoglycemia are comparable to those with placebo.

Incretin mimetics

- Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV.
- This effect is referred to as the "incretin effect" & is markedly reduced in type 2 diabetes.
- The incretin effect occurs because the gut releases incretin hormones, notably GLP-1 & gastric inhibitory polypeptide, in response to a meal.
- Incretin hormones are responsible for 60 - 70 % of postprandial insulin secretion.

Exenatide

- Injectable (SC) incretin mimetics.
- Used as adjunct therapy in patients with type 2 diabetes who have failed to achieve adequate glycemic control on **SU**, **metformin**, **glitazone** or their combination.

Mechanism of action

- Analogs of GLP-1, acting as GLP-1 receptor agonists & thus it:
  1. Improves glucose- dependent insulin secretion.
  2. Slows gastric emptying time, decrease food intake.
  3. Decreases postprandial glucagon secretion.
  4. Promotes β-cell proliferation.
- Consequently, weight gain & postprandial hyperglycemia are reduced & HbA1c levels decline.

Pharmacokinetics and fate

- Being polypeptide, **exenatide** must be administered SC.
- Because of its short duration of action, **exenatide** should be injected twice daily within 60 minutes prior to morning & evening meals.
- A once-weekly preparation is under investigation.
- Should be avoided in patients with severe renal impairment.

Adverse effects

- Similar to **pramlintide**, they consist of nausea, vomiting, diarrhea.