Oral agents:
1. **Oral agents: 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 type 1 diabetes.

A. Sulfonylureas (SUs)
These agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas. The primary drugs used today are tolbutamide (1st generation) & the 2nd generation drugs glyburide (glibenclamide), glipizide & glimepiride.

**Mechanism of action:**
1) Stimulation of insulin release from the β cells of the pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization & Ca2+ influx;
2) Reduction in hepatic glucose production
3) Increase in peripheral insulin sensitivity.

**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 Tolbutamide (6-12 hours), while that of 2nd generation is ranged from 12 to 24 hours.

**Adverse effects:**
- Propensity to cause weight gain, hyperinsulinemia & hypoglycemia.
- Used with caution in patients with hepatic or renal insufficiency.
- Renal impairment is a particular problem in the case of those agents that are metabolized to active compounds such as glyburide.
- Glyburide has minimal transfer across the placenta and may be a reasonably safe alternative to insulin therapy during pregnancy.

**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, Monoamine oxidase inhibitors, 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 in improving glycemic control.
- 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.
- Both glinides are metabolized to inactive products by cytochrome P450 in the liver & are excreted through the bile.

Adverse effects:
- Incidence of hypoglycemia is lower than that with SUs.
- Repaglinide effect may enhance by ketoconazole, itraconazole, fluconazole, erythromycin & clarithromycin, whereas opposed by other drugs, such as barbiturates, carbamazepine & rifampin.
- Repaglinide has been reported to cause severe hypoglycemia when taken concomitantly with gemfibrozil (lipid-lowering drug) & concurrent use is contraindicated.
- Weight gain is less than with the SUs.
- Used with caution in patients with hepatic impairment.

2. Oral agents: Insulin sensitizers
- Two classes biguanides & thiazolidinediones.
- They lower blood sugar by improving 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.
- Does not promote insulin secretion thus, 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. Also, it 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 to 6 weeks of use.
   - The patient commonly loses weight because of loss of appetite.
   - It is 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 production of glucose by the liver).

Pharmacokinetics and fate:
- Well absorbed orally, is not bound to serum proteins and is 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 with caution 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)
- They do not promote insulin release from the pancreatic β cells, so hyperinsulinemia is not a risk.
- Troglitazone was the first TZD but was withdrawn after a number of deaths from hepatotoxicity.
The two members of this class currently available are pioglitazone & rosiglitazone.

Mechanism of action:
- Exact mechanism by which the TZDs lower insulin resistance remains to be elucidated, but they are known to target the peroxisome proliferator–activated receptor-\(\gamma\) (PPAR\(\gamma\)), a nuclear hormone receptor.
- Ligands for PPAR\(\gamma\) 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 levels are neither affected by pioglitazone monotherapy nor when the drug is used in combination with other agents, whereas LDL levels have increased with 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 2\textsuperscript{nd} 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 dosage adjustment is required in renal impairment.
- It is recommended that these agents not be used in nursing mothers.

Adverse effects:
- Due to deaths from hepatotoxicity in patients 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.
- Increased 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 to resume in premenopausal women with polycystic ovary syndrome.

3. Oral agents: \( \alpha \)-Glucosidase inhibitors

**Acarbose & miglitol**

Orally active drugs used for the treatment of patients with 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 \( \alpha \)-glucosidase in the intestinal brush border (an enzyme responsible for the hydrolysis of oligosaccharides to glucose & other sugars).
- **Acarbose** also inhibits pancreatic \( \alpha \)-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:** It is important that the hypoglycemic patient 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.
- Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

4. Oral agents: 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, which is responsible for 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.
- Absorption does not affect by food.
- Majority of sitagliptin is excreted unchanged in the urine.
- Dosage adjustments is recommended for patients with renal dysfunction.

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 for the treatment of patients with type 2 diabetes.
- Used as adjunct therapy in patients 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.
- Slows gastric emptying time, decrease food intake.
- Decreases postprandial glucagon secretion.
- 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.