Drug	MOA& Uses	Pharmacokinetics	ADRs & Contraindications
Insulin secretagogues			
1-Sulfonylureas **First generation** **Tolbutamide (Short Acting)** safe for old diabetic patients or patients with renal impairment. second generation **A)Glipizide (Short Acting)** **B)glibenclamide (Glyburide)** **C)Glimepiride (Both Long-Acting)** ✓ **More** potent **than** first generation ✓ **Have** longer duration **of action.** ✓ **Less frequency of administration** ✓ **Have** fewer adverse effects ✓ **Have fewer drug interactions**	✓ Stimulate insulin release from functioning **B** cells by **blocking of ATP-sensitive K channels** which causes depolarization and opening of voltage- dependent calcium channels, which causes an increase in intracellular calcium in the beta cells, which stimulates insulin release. – **monotherapy or in combination with other oral hypoglycemic drugs**	✓ **Orally,** well absorbed. ✓ Reach peak concentration after 2-4 hr. ✓ All are **highly bound to plasma proteins.** ✓ Duration of action is variable. ✓ **Second generation** has longer duration than first generation. ✓ **Metabolized in liver** ✓ Excreted **in urine** (elderly and renal disease) ✓ **Cross placenta,** stimulate fetal β-cells to release insulin → fetal hypoglycemia at birth.	**1. Hyperinsulinemia & Hypoglycemia:** – **Less in tolbutamide.** – **More in long acting sulfonylureas.** – **More in old age, hepatic or renal diseases.** **2. Weight gain due to increase in appetite**
2-Meglitinides **Repaglinide** are rapidly acting insulin secretagogues	**Insulin secretagogue as sulfonylureas.** ✓ Type II diabetes: – monotherapy or in combination with other oral hypoglycemic drugs ✓ Patients allergic to sulfur or sulfonylureas	✓ Orally, well absorbed. ✓ **Very fast onset of action**, peak 1 h. ✓ short duration of action (4 h). ✓ Metabolized in liver and excreted in bile. ✓ Taken just before each meal (3 times/day).	✓ **Less incidence than sulfonylureas** ✓ **Hypoglycemia.** ✓ **Weight gain.**
Insulin sensitizers			
1-Biguanides **Metformin** **Advantages:** ● No risk of hypoglycemia ● No weight gain ● Improvement of lipid profile ● Inexpensive	✓ **Increases peripheral glucose utilization (tissue glycolysis)** ✓ **Reduces insulin resistance.** ✓ **Inhibits hepatic gluconeogenesis.** ✓ **↓LDL&VLDL** ✓ **↑ HDL** ● **overweight patients with type 2 diabetes *(first-line therapy).*** ● **Type II diabetes as monotherapy or in combination.**	✓ **orally.** ✓ **NOT bound to serum protein.** ✓ **NOT metabolized.** ✓ **t ½ 3 hours.** ✓ **Excreted unchanged in urine**	✓ **GIT disturbances:** nausea, vomiting, diarrhea ✓ **Lactic acidosis** ✓ Interference with vitamin B_{12} absorption (long term use). ✓ Metallic taste in the mouth ● Renal disease. ● Liver disease. ● Alcoholism. ● Cardiopulmonary dysfunction. ● Pregnancy.
2-Thiazolidinediones (glitazones) **Pioglitazone** ● Type II diabetes with insulin resistance. ● Used either alone or combined with sulfonylurea, biguanides or insulin. ● No risk of hypoglycemia when used alone	– **Activate peroxisome proliferator-activated receptor -γ (PPAR-γ).** – **Increase glucose uptake and utilization in muscle and adipose tissue.** – **Increase sensitivity of target tissues to insulin.**	– **Orally (once daily dose).** – **Highly bound to plasma albumins (99%)** – **Slow onset of activity** – **Half life 3-4 h** – **Metabolized in liver .** – **Excreted in urine 64% & bile**	● **Hepatotoxicity (liver function tests for 1st yearof therapy).** ● **Fluid retention (Edema).** ● **Congestive heart failure** ● **Mild weight gain.**

Drug	MOA& Uses	Pharmacokinetics	ADRs & Contraindications
Others			
1-Alpha glucosidase inhibitors A)Acarbose B) Miglitol	✓ Reversible inhibitors of intestinal α-glucosidases in intestinal brush border that are responsible for carbohydrate digestion. ✓ decrease carbohydrate digestion and glucose absorption in small intestine (lower postprandial glucose level). ● are effective alone in the earliest stages of impaired glucose tolerance. ● are not recommended alone as therapy for moderate to severe hyperglycemia ● are most useful in combination with other oral hypoglycemic drugs or with insulin . ● Taken just before meals. ● No hypoglycemia if used alone.	● Given orally ● Are not absorbed. ● Excreted in feces	✓ GIT side effects: Flatulence, diarrhea, abdominal pain, bloating, increase in liver enzymes. ● irritable bowel syndrome ● Inflammatory bowel disorders ● Intestinal obstruction.
2-Incretin mimetics – Exenatide	✓ is glucagon-like peptide-1 (GLP-1) agonist. ● Therapy of patients with type 2 diabetes who are not controlled with oral medicine.	● given s.c. once or twice daily	Nausea & vomiting (most common)
3-Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors) Sitagliptin	✓ Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1). Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.	● Orally ● Given once daily	Nausea, abdominal pain, diarrhea Nasopharyngitis

- **Incretins** are **GI hormones** secreted in response to food even before **blood glucose** level **becomes elevated.**
- Increase insulin secretion & decrease in glucagon secretion *(regulate blood glucose).*
- **Incretins include:**
  - **GLP-1 (glucagon-like peptide-1)**
  - **GIP (gastric inhibitory peptide)**
- Both are inactivated by **dipeptidyl peptidase-4 (DPP-4).**

Summary

- **1-Insulin secretagogues:** are drugs which increase the amount of **insulin secreted** by the pancreas. (Depend on functioning β cells, and thus are not effective in type I Diabetes)
- **Insulin secretagogues** include both **Sulfonylureas** and **Meglitinides,** and they both act on stimulating insulin release by **blocking of ATP-sensitive K channels**
- **Sulfonylureas** have variable durations of action with **second generation** having longer durations.
- Both generations are **metabolized in the liver** and **excreted in the Kidney.** This is of concern with elderly and patients with renal impairment.
- These drugs may also pass the placenta and cause fetal hypoglycemia, so regular insulin is used instead.
- **Tolbutamide** is the most used sulfonylurea because it is safe for old diabetic patients or patients with renal impairment (because it has a short duration of action with inactive metabolites).
- **Second generation sulfonylureas** (e.g. **Glibenclamide/ Glyburide**) are Contraindicated in hepatic impairment or renal insufficiency.
- sulfonylureas are used in Type II diabetes as **monotherapy** or in combination with other antidiabetic drugs.
- **ADRs:** hyperinsulemia, hypoglycemia, and weight gain.
- **Repaglinide (a Meglitinide analogues)** is also an acting insulin secretagogues that is used to control postprandial glucose levels and is used as monotherapy in managing diabetes type 2 or when patients are allergic to sulfur or sulfonylurea.

- **Metformin's (a biguanide)** main actions are increases glucose uptake and use by target tissues (insulin sensitization) and Inhibiting gluconeogenesis. **Insulin** has to be in certain amounts for it to give an effect.
- **Metformin** is excreated unchanged in the urine
- **It is used in obese patients as monotherapy** or combined therapy.
- **ADRs :** include: metallic taste, GIT disturbances (most common), and **increased rate of lactic acidosis (lethal).**
- **Contraindications**: 1) Pregnancy 2) Renal disease (excretion toxicity) 3) Liver disease 4) Alcoholism. 5) Conditions predisposing to hypoxia: cardiopulmonary dysfunction because of an increased risk of lactic acidosis induced by biguanide drugs
- **Thiazolidinediones (glitazones):** E.g. **Pioglitazone** are insulin sensitizers that are used as monotherapy or combined with other drugs, but have the adverse effects of hepatotoxicity and predisposition to congestive heart failure.
- **α- Glucosidase inhibitors: are** Reversible inhibitors of **intestinal α-glucosidases** in intestinal brush border responsible for degradation of oligosaccharides to monosaccharides and are poorly absorbed and mostly is excreated in stool. The unabsorbed sugars maybe fermented by insteinal bacteria to cause flatulence, diharreha, and abdominal pain.
- **Incretins** are GI hormones secreted in response to food even before blood glucose level becomes elevated. They are deactivated by dipeptidyl peptidase-4 (DPP-4).
- **Exenatide** [an incretin memtic given s.c. (Polypeptide)] is used as adjunctive therapy in patients with type 2 diabetes
- Sitagliptin Inhibit **DPP-4 enzyme** (enzyme responsible for incretin breakdown) and leads to an increase in incretin hormones level (*gastrointestinal hormone secreted in response to food*) → increase in insulin secretion & decrease in glucagon secretion.
- Sitagliptin is used in Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.
- **It's Adverse effects include:** GIT disturbance and Nasopharyngitis

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas Tolbutamide ,Glipizide Glibenclamide (glyburide)	Stimulating insulin production by inhibiting the KATP channel	Pancreatic beta cells	Effective Inexpensive	Hypoglycemia Weight gain
Meglitinides: repaglinide	Stimulates insulin secretion	Pancreatic beta cells	Sulfa free	Hypoglycemia,Weight gain
Biguanides :Metformin	Decreases insulin resistance	Liver	mild weight loss, No hypoglycemia	GIT symptoms,**Lactic acidosis ,Metallic taste**
Thiazolidinediones :pioglitazone	Decreases insulin resistance	Fat, muscle		Hepatoxicity ,Edema
α-Glucosidase inhibitors: Acarbose	Inhibits α-glucosidase	GI tract	Low risk	GI symptoms, flatulence
DPP-4 inhibitor :Sitagliptin	Increase incretin	GI tract		

Important strategy in choosing the appropriate drug:

- Prone diabetic→ insulin sensitizer (metformin)
- **Diabetic** →1-First choice are insulin sensitizers

2-is Combination (drug sensitizer –metformin-+ drug secretagogue – sulfonylureas -)

3- Insulin –if not controlled-