Oral Hypoglycemic

Drug Type	MOA	Pharmacokinetics	Uses	Side effect	Contraindication
1.Insulin Secretagogues					
a)Sulfonylureas: **1st G.→ Tolbutamide –short**	On B cells by blocking of **ATP-sensitive K channels** → depolarization & opening of **voltage- dependent calcium channels** → insulin secretion. ↓ Serum glucagon conc. ↑ Tissue sensitivity to insulin.	**Orally**, well absorbed. Reach peak conc. after 2-4 hr. **Highly** bound to plasma proteins. Duration of action is short. Metabolized in liver. Excreted in urine. **Cross placenta, stimulate fetal β-cells to release insulin → fetal hypoglycemia at birth.**	**Tolbutamide** Safe for old diabetic patients or pts with renal impairment.	Short acting = less side effect.	
2nd G. → Glipizide -short **Glyburide UK &** **Glibenclamide USA-long**			**Advantages over 1st generation:** **More potent** than first generation (single dose). Have **longer duration** of action. Have **few er adverse effects**. Have **few er drug interactions.**	**Unwanted Effects:** 1. **Hyperinsulinemia & Hypoglycemia.** Less in **tolbutamide**. More in **old age**, hepatic or renal diseases. 2. Weight gain, due to ↑ appetite. 3. GIT upset.	**Contraindication:** Hepatic impairment or renal insufficiency → hypoglycemia. Pregnancy & lactation. **Type I diabetes.** **Ketoacidosis**, cause of slow onset.
b) Meglitinides **Repaglinide**	Like sulfa	Orally, well absorbed. **Very fast onset of action,** peak 1 h. Short duration of action (4 h). Metabolized in liver & excreted in bile. Taken just before each meal.	**Type II diabetes:** Monotherapy or combined with metformin (better). Patients allergic to sulfur.	Like sulf + Hypoglycemia. Weight gain.	
2. Insulin Sensitizers **↑the sensitivity of target organs to insulin** **a) Biguanides** **Metformin**	Does not require functioning B cells. ↑ Peripheral glucose utilization (tissue glycolysis). **Inhibits** hepatic gluconeogenesis. **Impairs** glucose absorption from GIT. ↓Plasma glucagon lvl. **Anti-Hyperlipidemia action.**	**Orally**. **NOT** bound to serum protein → **no** drug interaction. NOT metabolized. T ½ 3 hrs. Excreted unchanged in urine.	**Type II diabetes** particular, **In overweight & obese** people (with insulin resistance). Monotherapy or in combination. **Advantage:** No risk of hyperinsulinemia or **hypoglycemia** or w eight gain → cause no insulin release.	**GIT:** N & V & D. **Lactic acidosis:** in patients with **renal**, **liver**, **pulmonary** or **cardiac** diseases. **Long term** use interferes with vitamin B12 absorption. Metallic taste.	Pregnancy. **Renal disease.** **Liver disease.** **Alcoholism.** Conditions predisposing to hypoxia as cardiopulmonary dysfunction.

b)Thiazolidinediones **(Glitazones) Pioglitazone (Actos)**	Acts by binding to **PPAR-γ.** ↑ Glucose **uptake** & utilization in muscle & adipose tissue. ↑ **Sensitivity** of target tissues to insulin.	**Orally** (once daily). **Highly** bound to plasma albumins (99%). Slow onset of activity Half life 3-4 h Metabolized in liver. Excreted in urine 64% & bile.	**Type II diabetes** with **insulin resistance**. Either alone or combined with **sulfonylurea, biguanides** or **insulin**. No risk of **hypoglycemia** when used alone → cause no insulin release.	**Hepatotoxicity** (LFT) **Fluid retention** (Edema) Precipitate congestive heart failure. Mild weight gain caused by edema. **lactic acidosis** cause, ↑ glycolysis & gluconeogenesis	
3.other **a) α -Glucosidase inhibitors** **Acarbose**	**Reversibly** inhibits intestinal **α -glucosidases** in intestinal brush border → no degradation of oligosaccharides to monosaccharides → ↓ carbs digestion & absorption. ↓postprandial hyperglycemia.	Given **orally**, poorly absorbed. Taken before meals. Act on GIT. Metabolized by intestinal bacteria. Excreted in stool and urine.	Are effective alone in the earliest stages of **impaired glucose tolerance**. **Type II diabetics** (combined with **sulfonylurea**).	**GIT:** Flatulence, diarrhea, abd pain. No hypoglycemia if used alone.	
b)Dipeptidyl peptidase-4 (DPP- 4) inhibitors **Sitagliptin**	**Inhibits DPP-4 enzyme** & ↑ **incretins** secretion (GI hormones secreted in response to food) → ↑insulin secretion & ↓glucagon secretion.	**Orally.** Given once daily. Half life 8-14 h. ↓ dose in pts with renal impairment.	**Type II DM** as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.	Nausea, abd pain, diarrhea. **Nasopharyngitis.**	**Note: Dipeptidyl peptidase-4** is involved in degradation of **incretins** GI hormones.

NOTE
ALL oral hypoglycemic are contraindicated in pregnancy.