

Oral hypoglycemic drugs: Oral Antihyperglycemic Drugs

Antidiabetic drugs are used to manage blood glucose levels in individuals with diabetes mellitus, particularly type 2 diabetes mellitus. These drugs are broadly classified into **insulin preparations** and **non-insulin (oral and injectable) antidiabetic agents** .

1. Classification of Antidiabetic Drugs

A. Insulin Preparations

These are injectable agents used in both type 1 and type 2 diabetes mellitus. They replace or supplement endogenous insulin.

B. Non-Insulin Antidiabetic Agents

These are primarily used in type 2 diabetes mellitus and include oral and injectable medications. They work by different mechanisms to lower blood glucose levels.

Main classes include:

1. Insulin secretagogues
2. Insulin sensitizers
3. Alpha-glucosidase inhibitors
4. Dipeptidyl peptidase-4 (DPP-4) inhibitors
5. Sodium-glucose co-transporter 2 (SGLT2) inhibitors
6. Glucagon-like peptide-1 (GLP-1) receptor agonists (injectable)

2. Insulin Secretagogues

These agents stimulate pancreatic beta cells to secrete insulin. They include **sulfonylureas** and **meglitinide analogues** .

A. Sulfonylureas

Mechanism of Action:

They bind to and inhibit ATP-sensitive potassium channels on pancreatic beta cells, leading to calcium influx and subsequent insulin exocytosis.

Therapeutic Effects:

- Increase endogenous insulin secretion
- Reduce circulating glucagon levels
- Improve insulin sensitivity in peripheral tissues

Examples and Generations:

Generation	Drug Names	Half-Life	Duration of Action	Notes
First	Tolbutamide	4–5 hours	6–8 hours	Safer in elderly
	Chlorpropamide	24–40 hours	20–60 hours	Can cause SIADH and disulfiram reaction
Second	Glipizide	2–4 hours	10–16 hours	Taken 30 minutes before meals
	Glyburide (Glibenclamide)	<3 hours	12–24 hours	Once daily dosing
	Glimepiride	5–9 hours	12–24 hours	Well tolerated, once daily

Adverse Effects:

- Hypoglycemia (especially in elderly or patients with renal or hepatic impairment)
- Weight gain
- Gastrointestinal upset
- Disulfiram-like reaction with alcohol (especially chlorpropamide)
- Hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)
- Secondary failure due to beta-cell exhaustion

Contraindications:

- Type 1 diabetes mellitus
- Pregnancy
- Significant hepatic or renal dysfunction

Drug Interactions:

- **Increased effect with:** Non-steroidal anti-inflammatory drugs, sulfonamides, fluconazole, warfarin
- **Decreased effect with:** Thiazide diuretics, corticosteroids, enzyme inducers

B. Meglitinide Analogues

Examples: Repaglinide, Nateglinide

Mechanism of Action:

Similar to sulfonylureas, they block ATP-sensitive potassium channels in beta cells, but they have a **rapid onset and short duration** of action. This makes them effective for **postprandial glucose control**.

Pharmacokinetics:

- Rapid absorption and onset
- Short half-life (about 1 hour)
- Metabolized by liver enzyme CYP3A4

- Excreted via bile

Dosing: Taken before meals (usually three times daily)

Advantages:

- Lower risk of hypoglycemia compared to sulfonylureas
- Safe in patients with sulfonamide allergy

Adverse Effects:

- Mild hypoglycemia
- Weight gain
- Gastrointestinal disturbances

3. Insulin Sensitizers

These agents enhance the body's sensitivity to insulin without stimulating insulin secretion.

A. Biguanides (e.g., Metformin)

Mechanism of Action:

- Inhibits hepatic gluconeogenesis (glucose production by the liver)
- Enhances peripheral insulin sensitivity
- Reduces intestinal glucose absorption

Advantages:

- First-line agent for type 2 diabetes mellitus
- No weight gain; may induce weight loss
- Does not cause hypoglycemia when used alone

Adverse Effects:

- Gastrointestinal upset (nausea, diarrhea)
- Risk of lactic acidosis (especially in renal impairment or alcohol abuse)

Contraindications:

- Renal dysfunction (eGFR < 30 mL/min)
- Liver failure
- Heart failure
- Severe infection or hypoxia

B. Thiazolidinediones (e.g., Pioglitazone, Rosiglitazone)

Mechanism of Action:

They activate peroxisome proliferator-activated receptor gamma (PPAR-?), increasing transcription

of insulin-responsive genes that enhance insulin sensitivity.

Adverse Effects:

- Fluid retention and edema (may worsen heart failure)
- Weight gain
- Increased risk of bone fractures
- Pioglitazone has a possible association with bladder cancer

4. Alpha-Glucosidase Inhibitors

Examples: Acarbose, Miglitol

Mechanism of Action:

They inhibit intestinal brush-border enzymes that digest complex carbohydrates, leading to delayed carbohydrate absorption and reduced postprandial glucose rise.

Adverse Effects:

- Flatulence
- Diarrhea
- Abdominal discomfort
- Does not cause hypoglycemia when used alone

5. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Examples: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin

Mechanism of Action:

These agents inhibit DPP-4 enzyme, which degrades incretins (such as GLP-1), leading to:

- Increased glucose-dependent insulin secretion
- Suppression of glucagon release

Advantages:

- Well tolerated
- Oral once-daily dosing
- Minimal risk of hypoglycemia

Adverse Effects:

- Headache
- Nasopharyngitis
- Rare: Pancreatitis, joint pain, hypersensitivity reactions

6. Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors

Examples: Canagliflozin, Dapagliflozin, Empagliflozin

Mechanism of Action:

They block SGLT2 in the proximal renal tubules, reducing glucose reabsorption and increasing urinary glucose excretion.

Benefits:

- Weight loss
- Reduction in blood pressure
- Cardiovascular and renal protective effects (especially empagliflozin)

Adverse Effects:

- Genital mycotic infections
- Urinary tract infections
- Volume depletion
- Euglycemic diabetic ketoacidosis
- Risk of limb amputation (canagliflozin)

7. Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Examples: Exenatide, Liraglutide, Dulaglutide, Semaglutide

Mechanism of Action:

- Stimulates insulin release in a glucose-dependent manner
- Suppresses postprandial glucagon secretion
- Delays gastric emptying
- Promotes satiety

Advantages:

- Promotes weight loss
- Low risk of hypoglycemia
- Cardiovascular benefits (liraglutide, semaglutide)

Adverse Effects:

- Nausea and vomiting
- Pancreatitis
- Injection site reactions
- Possible risk of medullary thyroid carcinoma (in rodents)