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:

Medcrine

www.medcrine.com

Generation First	Drug Names Tolbutamide	Half-Life 4–5 hours	Duration of Action 6–8 hours	Notes 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

www.medcrine.com

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

Medcrine

www.medcrine.com

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)