Insulin and Oral Hypoglycemic Agents
## Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th><strong>Type 1</strong></th>
<th><strong>Type 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Usually during childhood or puberty</td>
<td>Commonly over age 35</td>
</tr>
<tr>
<td><strong>Nutritional status at time of onset</strong></td>
<td>Commonly undernourished</td>
<td>Obesity usually present</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>5% to 10% of diagnosed diabetics</td>
<td>90% to 95% of diagnosed diabetics</td>
</tr>
<tr>
<td><strong>Genetic predisposition</strong></td>
<td>Moderate</td>
<td>Very strong</td>
</tr>
<tr>
<td><strong>Defect or deficiency</strong></td>
<td>β cells are destroyed, eliminating the production of insulin</td>
<td>Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects</td>
</tr>
</tbody>
</table>

**Figure 25.2**

Comparison of type 1 and type 2 diabetes.
# Summary of Drugs Used in the Treatment of Diabetes

## Insulin
- Insulin aspart: Novolog
- Insulin detemir: Levemir
- Insulin glargine: Lantus
- Insulin glulisine: Apidra
- Insulin lispro: Humalog
- NPH insulin suspension: Humulin N, Novolin N
- Regular insulin: Humulin R, Novolin R

## Incretin Mimetic
- Exenatide: Byetta, Bydureon
- Liraglutide: Victoza

## Amylin Analog
- Pramlintide: Symlin

## Oral Agents
- Acarbose: Precose
- Alogliptin: Nesina
- Bromocriptine: Cycloset
- Canagliflozin: Invokana
- Colesevelam: Welchol
- Dapagliflozin: Farxiga
- Glimepiride: Amaryl
- Glipizide: Glucotrol
- Glyburide: Diabeta, Glynase Prestab
- Linagliptin: Tradjenta
- Metformin: Fortamet, Glucophage
- Miglitol: Glyset
- Nateglinide: Starlix
- Pioglitazone: Actos
- Repaglinide: Prandin
- Rosiglitazone: Avandia
- Saxagliptin: Onglyza
- Sitagliptin: Januvia
- Tolbutamide: TOLBUTAMIDE
Diabetes Treatment

• A person with type 1 diabetes must rely on exogenous insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c).

• The **goal of insulin therapy in type 1 diabetes** is to **maintain blood glucose as close to normal as possible and to avoid wide swings in glucose.**

• The use of home blood glucose monitors facilitates frequent **self-monitoring and treatment with insulin.**
Diabetes Treatment

• The goal in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications.

✓ Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes.

✓ Most patients require pharmacologic intervention with oral glucose-lowering agents.

✓ As the disease progresses, β-cell function declines and insulin therapy is often needed to achieve satisfactory glucose levels.
Figure 25.5
Duration of type 2 diabetes mellitus, sufficiency of endogenous insulin, and recommended sequence of therapy.
**Insulin and Insulin Analogs**

- **Insulin** [IN-su-lin] is a **polypeptide hormone** consisting of two peptide chains that are connected by disulfide bonds.
- It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both of which are secreted by the β cells of the pancreas.
- Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators.
- Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas.
- There, it is phosphorylated by glucokinase, which acts as a glucose sensor.
- The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP).
- The rise in ATP levels causes a blockade of K+ channels, leading to membrane depolarization and an influx of Ca2+.
- The increase in intracellular Ca2+ causes pulsatile insulin exocytosis.
INSULIN AND INSULIN ANALOGS

- **Mechanism of action**
  - *Exogenous insulin* is administered to replace *absent insulin secretion in type 1 diabetes* or to *supplement insufficient insulin secretion in type 2 diabetes*.

- **Pharmacokinetics and fate**
  - *Human insulin* is produced by *recombinant DNA technology using* strains of *Escherichia coli* or *yeast* that are genetically altered to contain the gene for human *insulin*.
  - *Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties*.
  - *Insulin preparations vary primarily in their onset* and duration of activity.
  - For example, *insulin lispro, aspart, and glulisine* have a faster onset and shorter duration of action than *regular insulin, because they do not aggregate or form complexes*.
  - *Dose, injection site, blood supply, temperature, and physical activity* can also affect the onset and duration of various *insulin preparations*.
• Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally.
• Therefore, it is generally administered by **subcutaneous injection.**
• [Note: In a hyperglycemic **emergency**, **regular insulin** is administered **intravenously** (IV).]
• **Continuous subcutaneous** insulin infusion (also called the **insulin pump**) is another method of insulin delivery.
• This method of administration may be more convenient for some patients, eliminating multiple daily injections of insulin.
• The pump is programmed to deliver a basal rate of insulin.
• In addition, it allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate intake and compensate for high blood glucose.
Adverse reactions to insulin

• **Hypoglycemia** is the most serious and common adverse reaction to insulin.
• Other adverse reactions include **weight gain**.
• **Local injection** site reactions, and **lipodystrophy**.
• Lipodystrophy can be minimized by rotation of injection sites.
• **Diabetics with renal insufficiency** may require a decrease in insulin dose.
Figure 25.6
Adverse effects observed with insulin. [Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.]
Insulin preparations

- Insulin preparations are classified as
  - Rapid.
  - Short.
  - Intermediate.
  - Long-acting.
- It is important that clinicians exercise caution when adjusting insulin treatment, paying strict attention to the dose and type of insulin.
Rapid-acting and short-acting insulin preparations

- Four preparations fall into this category:
  - **Regular insulin.**
  - **Insulin lispro [lis-proe].**
  - **Insulin aspart [as-part].**
  - **Insulin glulisine [gloo-LYSEeen].**

- **Regular insulin** is a **short-acting**, soluble, crystalline zinc insulin.

- **Insulin lispro, aspart, and glulisine** are classified as **rapid-acting insulins**.

- Modification of the amino acid sequence of **regular insulin** produces analogs that are rapid-acting insulins.

- For example, insulin lispro differs from regular insulin in that the lysine and proline at positions 28 and 29 in the B chain are reversed
- This modification results in more rapid absorption, a quicker onset, and a shorter duration of action after subcutaneous injection.
- Peak levels of insulin lispro are seen at 30 to 90 minutes, as compared with 50 to 120 minutes for regular insulin.
- Insulin aspart and insulin glulisine have pharmacokinetic and pharmacodynamic properties similar to those of insulin lispro.
- Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of insulin and to control postprandial glucose.
- They may also be used in cases where swift correction of elevated glucose is needed.
• Rapid- and short-acting insulins are usually used in conjunction with a longer-acting basal insulin that provides control of fasting glucose.

✓ **Regular insulin** should be injected **subcutaneously** 30 minutes before a meal, whereas

✓ Rapid-acting insulins are administered in the 15 minutes proceeding a meal or within 15 to 20 minutes after starting a meal.

• Rapid-acting **insulins** are commonly used in external **insulin pumps**, and they are suitable for **IV administration**, although **regular insulin is most commonly used** when the IV route is needed.
Intermediate-acting insulin

• **Neutral protamine Hagedorn (NPH)** insulin is an intermediate-acting insulin formed by the addition of zinc and protamine to regular insulin.
• [Note: Another name for this preparation is insulin isophane.]
• The combination with protamine forms a complex that is less soluble, resulting in **delayed absorption** and a longer duration of action.
• NPH insulin is used for basal (fasting) control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control.
• NPH insulin should be given **only subcutaneously (never IV)**, and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis).
Long-acting insulin preparations

✓ Insulin glargine [GLAR-geen] isoelectric point is lower than that of human insulin, leading to formation of a precipitate at the injection site that releases insulin over an extended period.

• It has a slower onset than NPH insulin and a flat, prolonged hypoglycemic effect with no peak.

✓ Insulin detemir [deh-TEE-meer] has a fatty acid side chain that enhances association to albumin.

• Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine.

• As with NPH insulin, insulin glargine and insulin detemir are used for basal control and should only be administered subcutaneously.

• Neither long-acting insulin should be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic profile.
Figure 25.7
Onset and duration of action of human *insulin* and *insulin* analogs. NPH = neutral protamine Hagedorn.
Insulin Combinations

• Various premixed combinations of human insulins, such as 70% NPH insulin plus 30% regular insulin, or 50% of each of these are also available.

• Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.
Standard Treatment Versus Intensive Treatment

- **Standard insulin** therapy involves **twice-daily** injections.

- **Intensive treatment** utilizes **three or more** injections daily with frequent monitoring of blood glucose levels.

- The ADA recommends a target mean blood glucose level of 154 mg/dL or less (HbA1c ≤ 7%), and intensive treatment is more likely to achieve this goal.

- [Note: Normal mean blood glucose is approximately 115 mg/dL or less (HbA1c < 5.7%).]

- The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive insulin regimens.
• Patients on intensive therapy show a significant reduction in **microvascular complications** of diabetes such as **retinopathy**, **nephropathy**, and **neuropathy** compared to patients receiving standard care.

• Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness.

• Intensive therapy has not been shown to significantly reduce macrovascular complications of diabetes.
Examples of three regimens that provide both prandial and basal insulin replacement.

*B* = breakfast; *L* = lunch; *S* = supper. NPH = neutral protamine Hagedorn
Intensive therapy results in a threefold increase in the frequency of hypoglycemia.

Many clinicians believe the increased risk of hypoglycemia that accompanies intensive therapy is justified by the substantial decrease in the incidence of long-term complications, such as diabetic retinopathy and nephropathy.

Figure 25.9
A. Effect of tight glucose control on hypoglycemic episodes in a population of patients with type 1 diabetes receiving intensive or standard therapy. B. Effect of standard and intensive care on the long-term complications of diabetes.
**Synthetic Amylin Analog**

- **Amylin** is a hormone that is cosecreted with insulin from β cells following food intake.
- It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety.
- **Pramlintide** [PRAM-lin-tide] is a *synthetic amylin analog* that is indicated as an adjunct to mealtime insulin therapy in patients with type 1 and type 2 diabetes.
- **Pramlintide** is administered by *subcutaneous injection immediately prior to meals*.
- When pramlintide is initiated, the dose of mealtime insulin should be decreased by 50% to avoid a risk of severe hypoglycemia.
- Other adverse effects include nausea, anorexia, and vomiting.
- **Pramlintide** may not be mixed in the same syringe with insulin, and it should be avoided in patients with diabetic gastroparesis (delayed stomach emptying), cresol hypersensitivity, or hypoglycemic unawareness.
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” and is markedly reduced in type 2 diabetes.

• The incretin effect occurs because the gut releases incretin hormones, notably glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide in response to a meal.

• Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion.

• **Exenatide** [EX-e-nah-tide] and **liraglutide** [LIR-a-GLOO-tide] are injectable incretin mimetics used for the treatment of type 2 diabetes.
Mechanism of action

• The incretin mimetics are analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists.

✓ These agents improve glucose dependent insulin secretion

✓ Slow gastric emptying time

✓ Reduce food intake by enhancing satiety (a feeling of fullness)

✓ Decrease postprandial glucagon secretion, and promote β-cell proliferation.

✓ Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline.
Pharmacokinetics and fate

• Being polypeptides, **exenatide** and **liraglutide** must be administered **subcutaneously**.

• Liraglutide is **highly protein bound and has a long half-life**, allowing for **once-daily** dosing without regard to meals.

• **Exenatide** is eliminated mainly via **glomerular filtration** and has a much shorter half-life.

• Because of the short duration of action, exenatide should be injected twice daily within 60 minutes prior to morning and evening meals.

• A **once-weekly extended-release preparation** is also available.

• **Exenatide** should be avoided in patients with severe renal impairment.
Adverse effects

- The main adverse effects of the incretin mimetics consist of **nausea, vomiting, diarrhea, and constipation**.

- **Exenatide** and **liraglutide** have been associated with **pancreatitis**.

- Patients should be advised to discontinue these agents and contact their health care provider immediately if they experience severe abdominal pain.

- **Liraglutide** causes thyroid C-cell tumors in rodents.

- It is unknown if it causes these tumors or thyroid carcinoma in humans.
Oral Agents

• **Oral agents** are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet.

• Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents.

• Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycemia.
Sulfonylureas

- These agents are classified as *insulin secretagogues*, because they promote insulin release from the β cells of the pancreas.
- The sulfonylureas in current use are the second-generation drugs *glyburide* [GLYE-byoor-ide], *glipizide* [GLIP-ih-zide], and *glimepiride* [GLYE-me-pih-ride].

Mechanism of action: The main mechanism of action includes

- Stimulation of insulin release from the β cells of the pancreas.
- Sulfonylureas block ATP-sensitive K+ channels, resulting in depolarization, Ca²⁺ influx, and insulin exocytosis.
- In addition, sulfonylureas may *reduce hepatic glucose production* and *increase peripheral insulin sensitivity*. 
• **Pharmacokinetics and fate:** Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted in the urine and feces.

• The **duration of action** ranges from **12 to 24 hours**.

• **Adverse effects:** Major adverse effects of the sulfonylureas are weight gain, hyperinsulinemia, and hypoglycemia.

✓ They should be used with caution in hepatic or renal insufficiency, since accumulation of sulfonylureas may cause hypoglycemia.

• **Renal impairment** is a particular problem for **glyburide**, as it may increase the duration of action and increase the risk of hypoglycemia significantly.

• **Glipizide** or **glimepiride** are safer options in renal dysfunction and in elderly patients.

• **Glyburide** has minimal transfer across the placenta and may be an alternative to insulin for diabetes in pregnancy.
Glinides

- This class of agents includes repaglinide [re-PAG-lin-ide] and nateglinide [nuh-TAY-gli-nide]. Glinides are also considered insulin secretagogues.

- **Mechanism of action:** Like the sulfonylureas, the glinides stimulate insulin secretion.
  - They bind to a distinct site on the β cell, closing ATP-sensitive K+ channels, and initiating a series of reactions that results in the release of insulin.
  - In contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators.

- Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.
  - This would increase the risk of serious hypoglycemia.
  - **Pharmacokinetics and fate:** Glinides should be taken prior to a meal and are well absorbed after oral administration. Both glinides are metabolized to inactive products by cytochrome P450 3A4 in the liver and are excreted through the bile.
Adverse effects:

- Although **glinides** can cause hypoglycemia and weight gain, the incidence is lower than that with sulfonylureas.
- **Drugs that inhibit CYP3A4**, such as itraconazole, fluconazole, erythromycin, and clarithromycin, may enhance the glucose lowering effect of **repaglinide**.
- **Drugs that induce CYP3A4**, such as barbiturates, carbamazepine, and rifampin, may have the opposite effect.
- By inhibiting **hepatic metabolism**, the lipid-lowering drug gemfibrozil may significantly increase the effects of **repaglinide**, concurrent use is contraindicated.
- These agents should be used with caution in patients with **hepatic impairment**.
Biguanides

- **Metformin** [met-FOR-min], the only biguanide, is classified as an **insulin sensitizer**.
- It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance.
- Unlike sulfonylureas, metformin does not promote insulin secretion.
- Therefore, hyperinsulinemia is not a problem, and the risk of hypoglycemia is far less than that with sulfonylureas.
Biguanides

- **Mechanism of action:** The main mechanism of action of metformin
  - *Is reduction of hepatic gluconeogenesis.* [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.]
  - **Metformin** also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization.
  - **Weight loss may occur because metformin causes loss of appetite.**
  - The ADA recommends metformin as the initial drug of choice for type 2 diabetes.
  - **Metformin may be used alone or in combination with other oral agents or insulin.**
  - Hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.
Pharmacokinetics and fate: Metformin is well absorbed orally, is not bound to serum proteins, and is not metabolized.

- Excretion is via the urine.

Adverse effects: These are largely gastrointestinal. Metformin is contraindicated in renal dysfunction due to the risk of lactic acidosis.

- Metformin should be used with caution in patients older than 80 years and in those with heart failure or alcohol abuse.

- Long-term use may interfere with vitamin B12 absorption.
Other uses: In addition to type 2 diabetes

- Metformin is effective in the treatment of polycystic ovary syndrome.
- It lowers insulin resistance seen in this disorder and can result in ovulation and, therefore, possibly pregnancy.
Thiazolidinediones

- The thiazolidinediones (TZDs) are also **insulin sensitizers**. The two members of this class are
  - **Pioglitazone** [pye-oh-gli-ta-zone] and
  - **Rosiglitazone** [roe-si-GLIH-ta-zone].
- Although insulin is required for their action, the TZDs do not promote its release from the β cells, so **hyperinsulinemia** is not a risk.
Mechanism of action: The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator–activated receptor-γ (PPARγ), a nuclear hormone receptor.

Activation of PPARγ regulates the transcription of several insulin responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.

Effects of these drugs on cholesterol levels are of interest.

- **Rosiglitazone increases** LDL cholesterol and triglycerides, whereas **pioglitazone decreases** triglycerides.

- **Both drugs increase** HDL cholesterol.
• The TZDs can be used as **monotherapy** or in **combination** with other glucose-lowering agents or insulin.

• The dose of insulin may have to be lowered when used in combination with these agents.

• The ADA recommends **pioglitazone** as a second- or third-line agent for type 2 diabetes.

• **Rosiglitazone** is less utilized due to concerns regarding cardiac adverse effects.
**Pharmacokinetics and fate:** *Pioglitazone and rosiglitazone are* well absorbed after **oral administration** and 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 active drug and metabolites excreted in the bile and eliminated in the feces.
- Metabolites of rosiglitazone are primarily excreted in the urine.
- **No dosage adjustment is required in renal impairment.**
- These agents should be avoided in nursing mothers.
• **Adverse effects:** A few cases of liver toxicity have been reported with these drugs, and periodic monitoring of liver function is recommended.

• **Weight gain** can occur because TZDs may increase subcutaneous fat and cause **fluid** retention.

• [Note: Fluid retention can worsen heart failure. These drugs should be avoided in patients with severe heart failure.]

• TZDs have been associated with osteopenia and **increased fracture risk.**

• Pioglitazone may also increase the risk of bladder cancer.
• Several meta-analyses identified a potential increased risk of **myocardial** infarction and death from cardiovascular causes with **rosiglitazone**.

• As a result, use of rosiglitazone was limited to patients enrolled in a special restricted access program.

• After a further review of safety data, the restrictions on rosiglitazone use were subsequently lifted.

• **Other uses:** As with metformin, the relief of insulin resistance with the TZDs can cause ovulation to resume in premenopausal women with polycystic ovary syndrome.
**α-Glucosidase inhibitors**

- **Acarbose** [AY-car-bose] and **miglitol** [MIG-li-tol] are oral agents used for the treatment of type 2 diabetes.

- **Mechanism of action:** Located in the intestinal brush border, α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed.
  - Acarbose and miglitol **reversibly inhibit** α-glucosidase enzymes.
  - When taken at the **start of a meal**, these drugs **delay the digestion** of carbohydrates, resulting in lower postprandial glucose levels.
  - Since they do not stimulate insulin release or increase insulin sensitivity, these agents **do not cause hypoglycemia** when used as monotherapy.
  - However, when used with insulin secretagogues or insulin, hypoglycemia may develop. [Note: It is important that hypoglycemia in this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]
Pharmacokinetics and fate: Acarbose is poorly absorbed.

- It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine.
- Miglitol is very well absorbed but has no systemic effects.
- It is excreted unchanged by the kidney.

Adverse effects: The major side effects are flatulence, diarrhea, and abdominal cramping.

- Adverse effects limit the use of these agents in clinical practice.
- Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.
Dipeptidyl peptidase-4 inhibitors

• **Alogliptin** [al-oh-GLIP-tin], **linagliptin** [lin-a-GLIP-tin], **saxagliptin** [saxa- GLIP-tin], and **sitagliptin** [si-ta-GLIP-tin] are orally active dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.

- **Mechanism of action:** These drugs inhibit the enzyme **DPP-4**, which is responsible for the inactivation of incretin hormones such as GLP-1.
  - Prolonging the activity of incretin hormones increases insulin release in response to meals and reduces inappropriate secretion of glucagon.
  - DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, metformin, TZDs, or insulin.
  - Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral.

- **Pharmacokinetics and fate:** The DPP-4 inhibitors are well absorbed after oral administration.
  - Food does not affect the extent of absorption.
  - All DPP-4 inhibitors except linagliptin require dosage adjustments in renal dysfunction.

- **Adverse effects:** In general, DPP-4 inhibitors are well tolerated, with the most common adverse effects being nasopharyngitis and headache.
  - Although infrequent, **pancreatitis** has occurred with use of all DPP-4 inhibitors.
Sodium–glucose cotransporter 2 inhibitors

- **Canagliflozin** [kan-a-gli-flo-e-zin]
- **Dapagliflozin** [dap-a-gli-flœzïn]

**Mechanism of action:** The sodium–glucose cotransporter 2

- (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose.
- Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis. Therefore, SGLT2 inhibitors may reduce systolic blood pressure. However, they are not indicated for the treatment of hypertension.

**Pharmacokinetics and fate:** These agents are given once daily in the morning.

- Canagliflozin should be taken before the first meal of the day.
- While the primary route of excretion for canagliflozin is via the feces, about one-third of a dose is renally eliminated.
- These agents should be avoided in patients with renal dysfunction.

**Adverse effects:** The most common adverse effects with SGLT2 inhibitors are female genital mycotic infections (for example, vulvovaginal candidiasis), urinary tract infections, and urinary frequency.
- **Hypotension** has also occurred, particularly in the elderly or patients on diuretics.
- Thus, volume status should be evaluated prior to starting these agents.
Other agents

• Both the dopamine agonist bromocriptine and the bile acid sequestrant colesevelam produce modest reductions in HbA1c.

• The mechanism of action of glucose lowering is unknown for both of these drugs.

• Their modest efficacy and adverse effects limit their use in clinical practice.
<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>MECHANISM OF ACTION</th>
<th>EFFECT ON PLASMA INSULIN</th>
<th>RISK OF HYPOGLYCEMIA</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Stimulates insulin secretion</td>
<td>↑</td>
<td>Yes</td>
<td>Well-established history of effectiveness. Weight gain can occur. Hypoglycemia most common with this class of oral agents.</td>
</tr>
<tr>
<td><em>Glimepiride</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Gliclazide</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Glyburide</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glinides</td>
<td>Stimulates insulin secretion</td>
<td>↑</td>
<td>Yes (rarely)</td>
<td>Taken with meals. Short action with less hypoglycemia. Postprandial effect.</td>
</tr>
<tr>
<td><em>Nateglinide</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Repaglinide</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Decreases hepatic production of glucose</td>
<td>↓</td>
<td>No</td>
<td>Preferred agent for type 2 diabetes. Well-established history of effectiveness. Weight loss may occur. Monitor renal function.</td>
</tr>
<tr>
<td><em>Metformin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones (glitazones)</td>
<td>Binds to peroxisome proliferator-activated receptor-γ in muscle, fat and liver to decrease insulin resistance</td>
<td>↓↑</td>
<td>No</td>
<td>Effective in highly insulin-resistant patients. Once-daily dosing for pioglitazone. Check liver function before initiation. Avoid in liver disease or heart failure.</td>
</tr>
<tr>
<td><em>Pioglitazone</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rosiglitazone</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Decreases glucose absorption</td>
<td>↔</td>
<td>No</td>
<td>Taken with meals. Adverse gastrointestinal effects.</td>
</tr>
<tr>
<td><em>Acarbose</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Miglitol</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Increases glucose-dependent insulin release; decreases secretion of glucagon</td>
<td>↑</td>
<td>No</td>
<td>Once-daily dosing. May be taken with or without food. Well tolerated. Risk of pancreatitis.</td>
</tr>
<tr>
<td><em>Alogliptin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Linagliptin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sitagliptin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Saxagliptin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td>Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety</td>
<td>↑</td>
<td>No</td>
<td>Injection formulation. Exenatide should be injected twice daily within 60 minutes prior to morning and evening meals. Extended-release exenatide is given once weekly. Liraglutide is dosed once-daily without regard to meals. Weight loss may occur. Risk of pancreatitis.</td>
</tr>
<tr>
<td><em>Exenatide</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Liraglutide</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Increases urinary glucose excretion</td>
<td>↔</td>
<td>No</td>
<td>Once-daily dosing in the morning. Risk of hypotension, hyperkalemia. Avoid in severe renal impairment.</td>
</tr>
<tr>
<td><em>Canagliflozin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Dapagliflozin</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 25.13*
Summary of oral agents used to treat diabetes. ↔ = little or no change. DPP-4 = dipeptidyl peptidase-4.
Figure 25.14
Treatment guidelines for type 2 diabetes.