Drugs for DM

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INSULIN PREPARATIONS AND TREATMENT/A. Rapid-acting and short-acting insulin preparations

Four preparations fall into this category: **regular insulin, insulin lispro , insulin aspart, and insulin glulisine.**

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

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

Peak levels of insulin lispro are seen at 30 to 90 minutes, as compared with 50 to 120 minutes for regular insulin.

commonly used when the IV route is needed.

INSULIN PREPARATIONS AND TREATMENT/A. Rapid-acting and short-acting insulin preparations

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.

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.

INSULIN PREPARATIONS AND TREATMENT/ B. Intermediate-acting insulin

Neutral protamine Hagedorn (NPH) insulin is an intermediate-acting insulin formed by the addition of **zinc and protamine** to regular insulin.

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).

INSULIN PREPARATIONS AND TREATMENT/ C. Long-acting insulin preparations

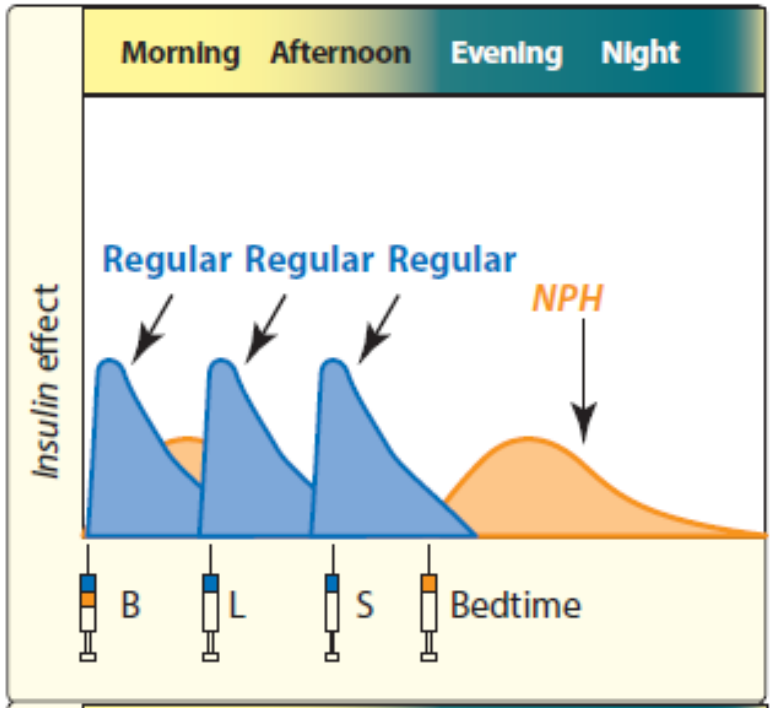
The isoelectric point of **insulin glargine** is lower than that of human insulin, leading to formation of a precipitate at the injection site that releases insulin over an extended period.

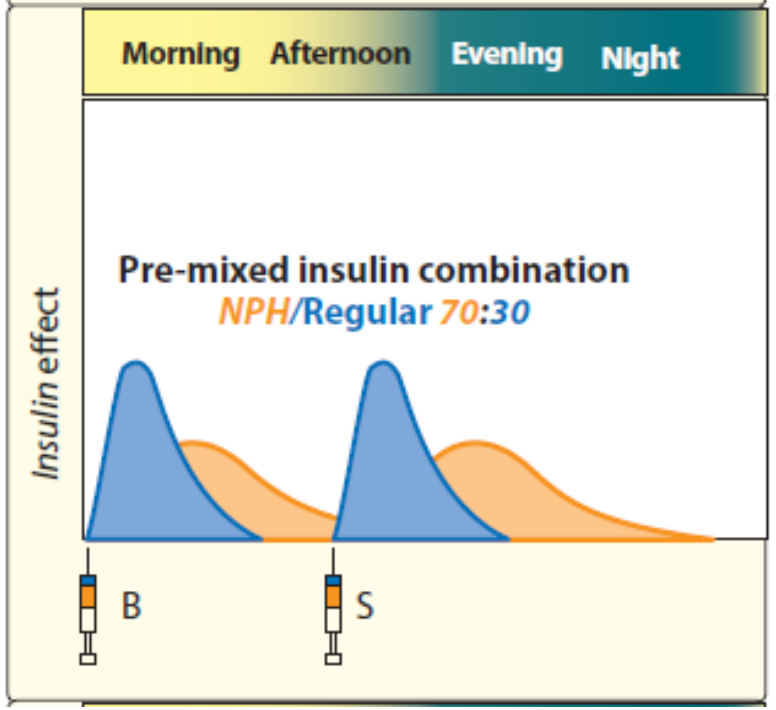
It has a **slower onset** than NPH insulin and a flat, prolonged hypoglycemic effect with no peak.

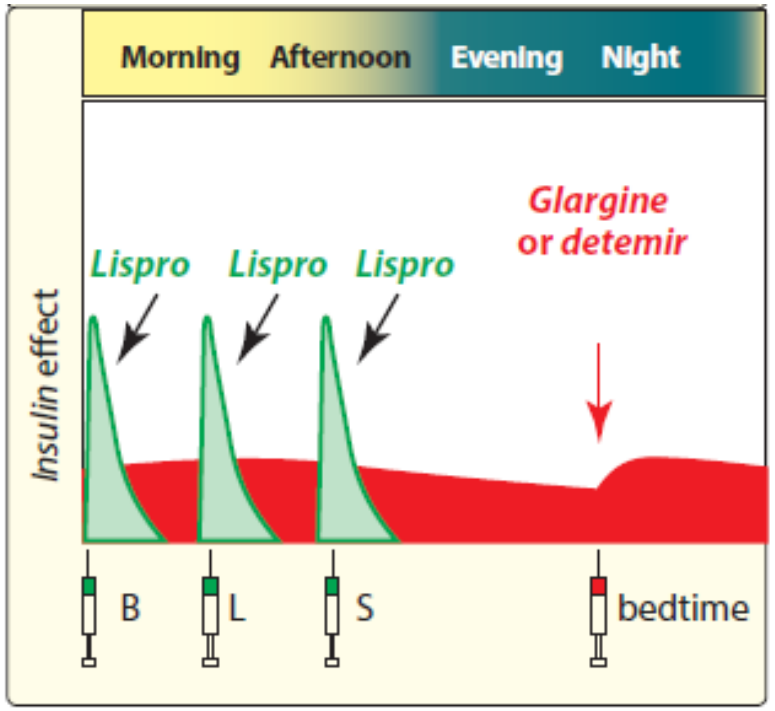
Insulin detemir has a fatty acid side chain that enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine.

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.







Examples of three regimens that provide both prandial and basal insulin replacement. B = breakfast; L = lunch; S = supper. NPH = neutral protamine Hagedorn.

INSULIN PREPARATIONS AND TREATMENT/ D. 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.

INSULIN PREPARATIONS AND TREATMENT/ E. Standard treatment versus intensive treatment

Standard insulin therapy involves twice-daily injections.

In contrast, **intensive treatment** utilizes **three or more** injections daily with frequent monitoring of blood glucose levels.

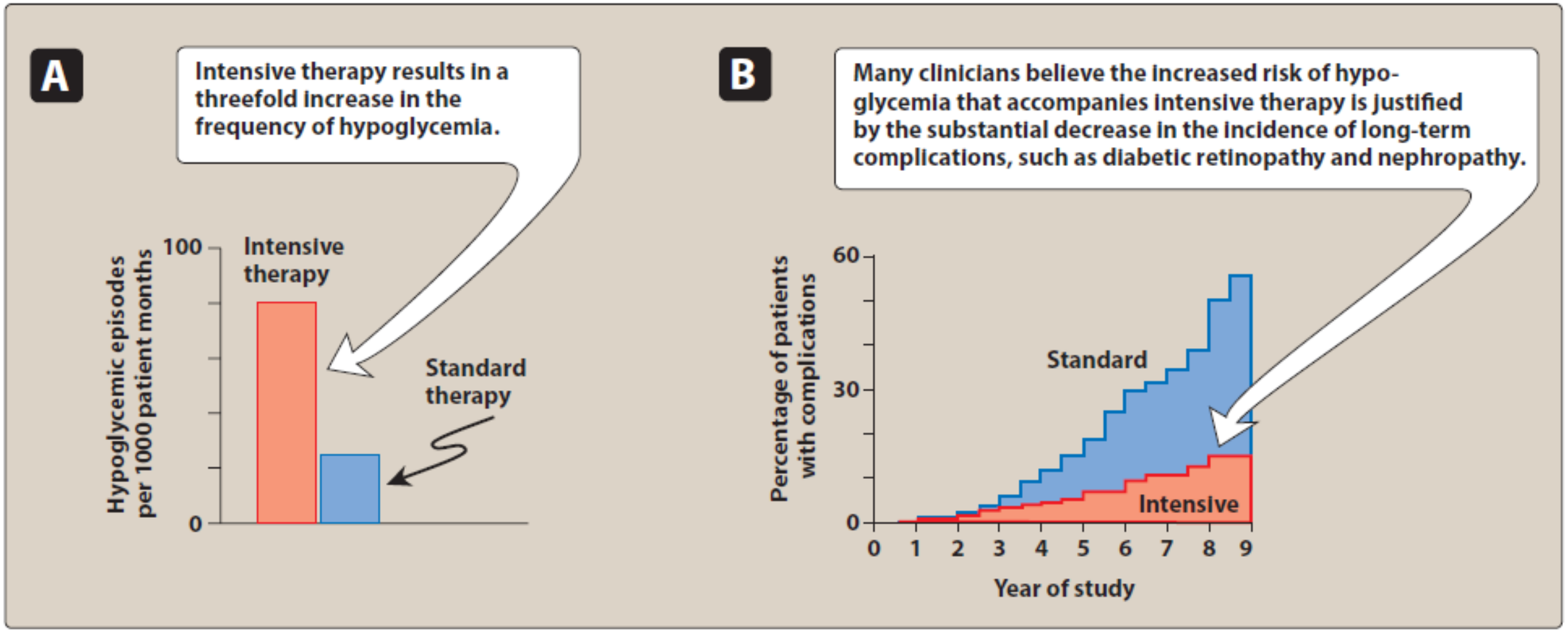
It is recommended the target of mean blood glucose level is 154 mg/dL or less (HbA1c ≤ 7%), and intensive treatment is more likely to achieve this goal.

However, 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.

INSULIN PREPARATIONS AND TREATMENT/ E. Standard treatment versus intensive treatment

Intensive therapy should not be recommended for patients with significant **microvascular** complications, **advanced age**, and those with **hypoglycemic** unawareness.

Intensive therapy has not been shown to significantly reduce macrovascular complications of diabetes.



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**.

V. 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 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) or **hypoglycemic** unawareness.

VI. INCRETIN MIMETICS

Oral glucose results in a higher secretion of insulin that 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 and liraglutide are injectable incretin mimetics used for the treatment of type 2 diabetes.

VI. INCRETIN MIMETICS/ A. 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.

VI. INCRETIN MIMETICS/ B. 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.

VI. INCRETIN MIMETICS/ C. 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**. However, it is unknown if it causes these tumors or thyroid carcinoma in humans.

VII. 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.

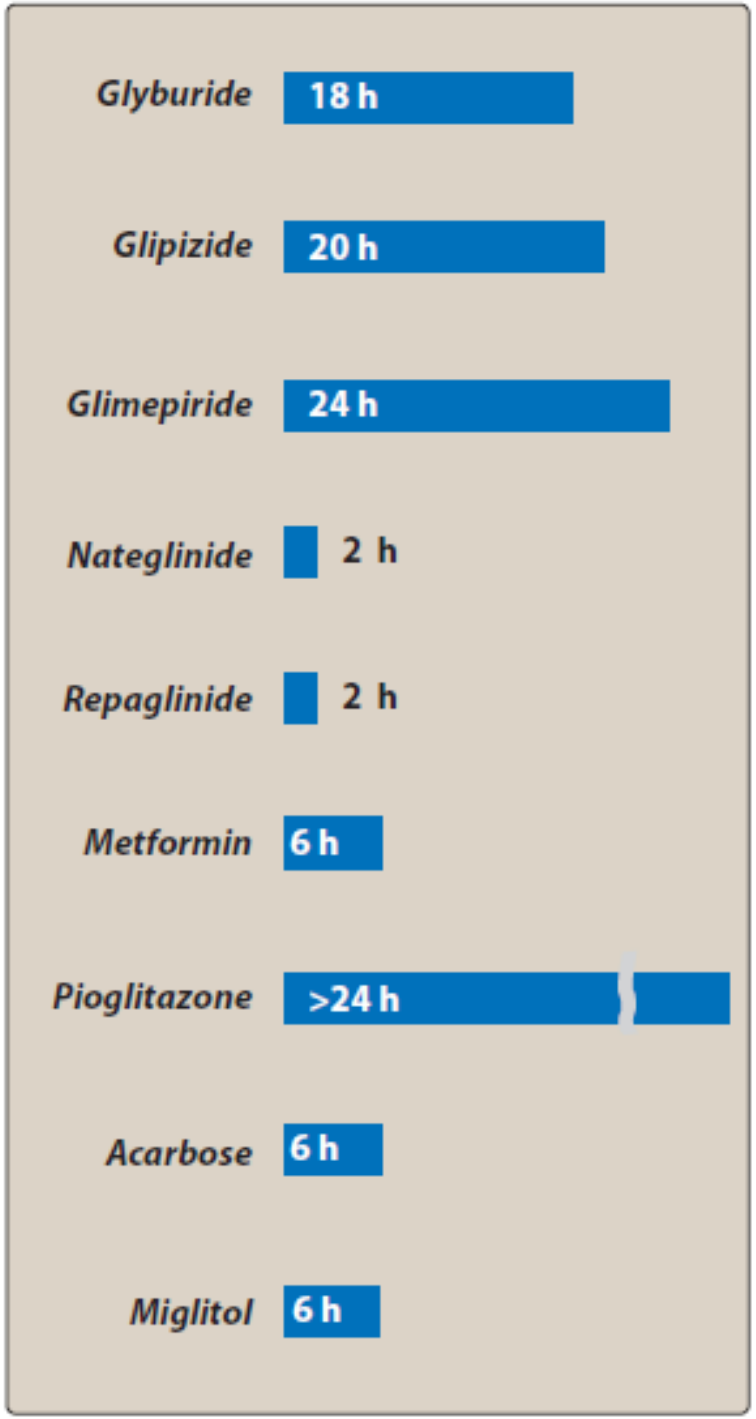
Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycemia.

Figure 25.10 summarizes the duration of action of some of the oral glucose-lowering drugs, and Figure 25.11 illustrates some of the common adverse effects.

VII. ORAL AGENTS/ A. 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, glipizide, and glimepiride.



Duration of action of some of the oral glucose-lowering drugs,

VII. ORAL AGENTS/ A. Sulfonylureas/ 1. Mechanism of action:

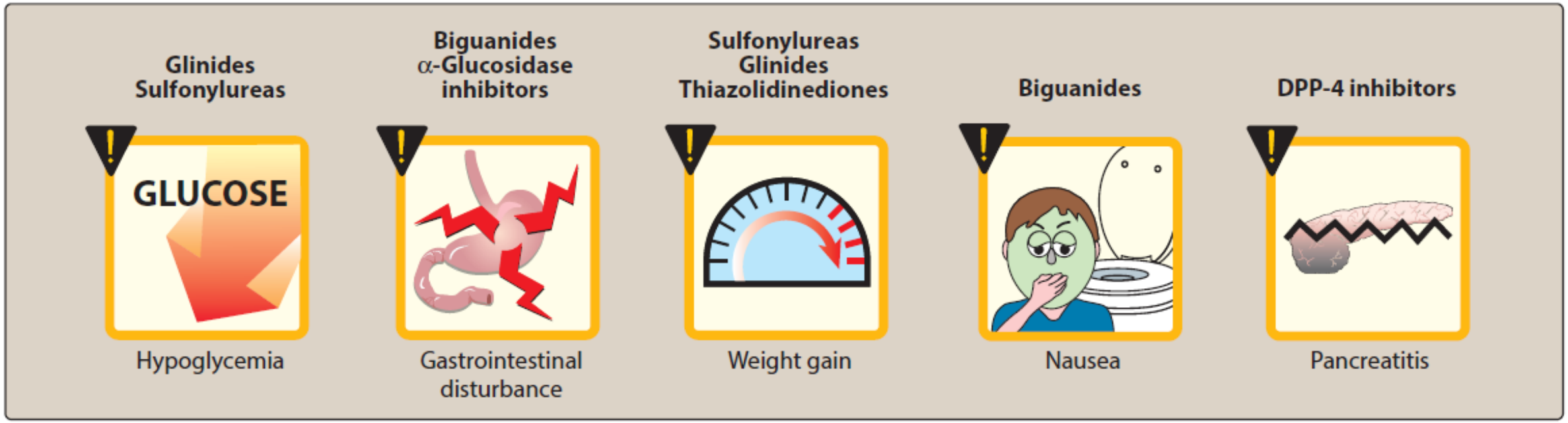
The main mechanism of action includes **stimulation of insulin release** from the β cells of the pancreas.

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**

2. 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.

VII. ORAL AGENTS/ A. Sulfonylureas/ 3. Adverse effects:



Some adverse effects observed with oral hypoglycemic agents.

VII. ORAL AGENTS/ A. Sulfonylureas/ 3. Adverse effects:

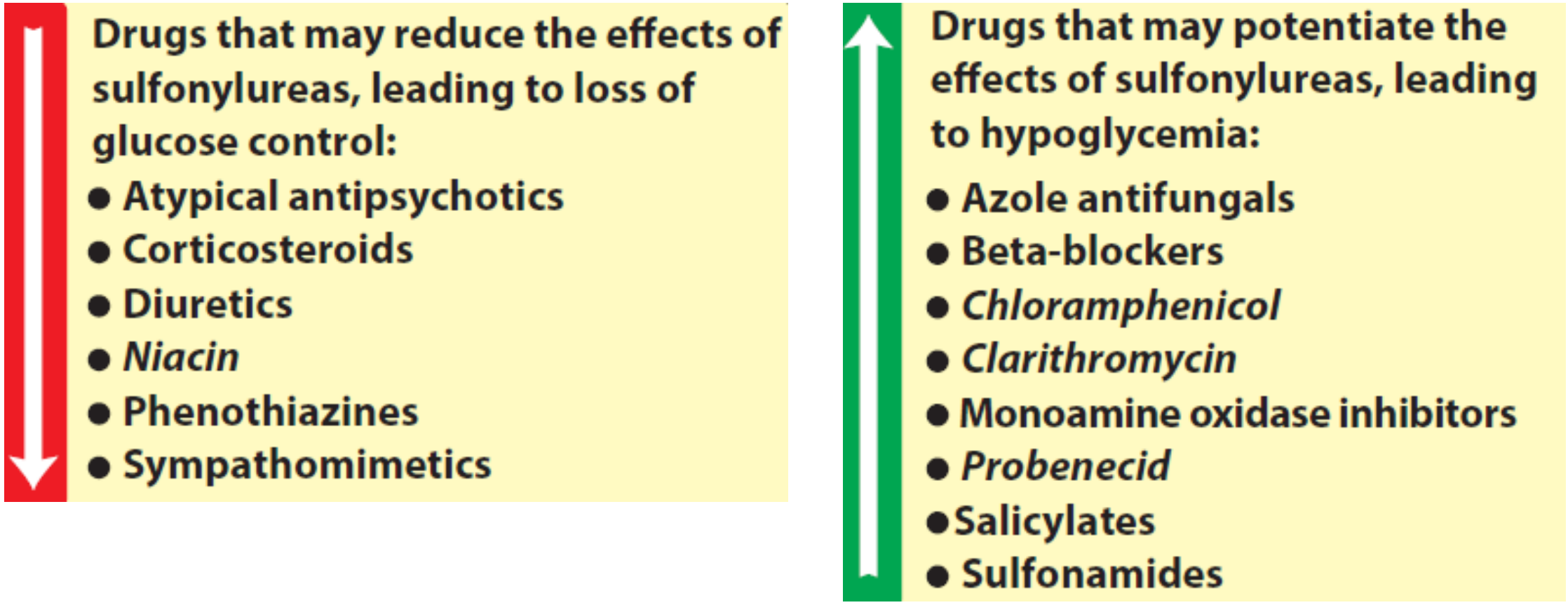
Major adverse effects of the sulfonylureas are **weight gain, hyperinsulinemia, and hypoglycemia.**

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.



Drugs interacting with sulfonylureas

VII. ORAL AGENTS/ B. Glinides/ 1. Mechanism of action:

This class of agents includes **repaglinide and nateglinide** . Glinides are also considered insulin **secretagogues**. 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.

VII. ORAL AGENTS/ B. Glinides/ 2. 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.

VII. ORAL AGENTS/ B. Glinides/ 3. Adverse effects:

Although glinides can cause hypoglycemia and weight gain, the **incidence is lower than that with sulfonylureas.**

[Note: Drugs that inhibit CYP3A4, such as itraconazole, fluconazole, erythromycin, and clarithromycin, may enhance the glucoselowering 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, and concurrent use is contraindicated.

These agents should be used with caution in patients with hepatic impairment.