TABLE 66-7 NON-INSULIN ANTIDIABETIC AGENTS BY DRUG CLASS*

DRUG CLASS	AVAILABLE AGENTS (GENERIC NAME)	ROUTE OF ADMINISTRATION	MODE OF ACTION
Biguanides	Metformin	Oral	Insulin sensitizer
Sulfonylureas	Glipizide, glyburide, glimeperide, gliclazide, chlorpropamide, tolazamide	Oral	Insulin secretagogue
Meglitinides	Repaglinide, nateglinide	Oral	Insulin secretagogue
Thiazolidinediones	Pioglitazone, rosiglitazone	Oral	Insulin sensitizer
GLP-1 analogues	Exenatide, liraglutide, albiglutide	Subcutaneous injection	Incretin mimetic
DPP-4 inhibitors	Sitagliptin, saxagliptin, linagliptin, alogliptin	Oral	Incretin amplifier
α-Glucosidase inhibitors	Acarbose, miglitol	Oral	Delay carbohydrate digestion/absorption
Amylin mimetics	Pramlintide	Subcutaneous injection	Delay gastric emptying, suppress glucagon
SGLT2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin	Oral	Increase urinary glucose excretion

DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transport protein subtype 2.
*Consult current manufacturer information for details on available combinations, prescribing, and safety.

consulted before prescribing these drugs to ensure updated and adequately detailed information on available single and combination agents and their effective and safe use.

Metformin

Metformin is an oral agent in the biguanide class that produces its most prominent effects by decreasing gluconeogenesis and thus reducing hepatic glucose production. This insulin-sensitizing effect is associated with a low risk of hypoglycemia. It has been in use for more than 30 years and is available in inexpensive generic form. The usual starting dose is 500 mg once or twice daily with incremental advancement at several-week intervals to a usual maximum of 2000 mg daily in two or three divided doses. Metformin typically decreases HbA_{1c} by about 1.5%. Further benefits include modest weight loss (approximately 3 kg on average) and a small improvement in plasma lipid profile (decrease in low-density lipoprotein [LDL]-cholesterol and triglycerides and increase in HDL). Adverse reactions include gastrointestinal effects and, rarely, lactic acidosis. The drug should be avoided in patients with renal insufficiency.

Sulfonylureas

Sulfonylureas stimulate endogenous insulin secretion by binding and activating potassium channels in beta cells. In patients with adequate residual beta cell function, they can lower HbA_{1c} levels by 1% to 2%. Drugs in this class have been in clinical use for more than 40 years, and many inexpensive, generic sulfonylureas are available that differ in duration of action, metabolism, and mode of clearance. Because they can increase insulin secretion even in the absence of hyperglycemia, they have significant potential to cause hypoglycemia. Patients need to be instructed how to recognize and treat hypoglycemia before starting a sulfonylurea. Factors that increase the risk for hypoglycemia with sulfonylureas include advanced age, poor nutrition, alcohol ingestion, and hepatic and renal insufficiency. Other disadvantages of this drug class are a tendency to cause weight gain and a loss of effectiveness over time.

Meglitinides

Repaglinide and nateglinide activate beta cell potassium channels and thus stimulate endogenous insulin secretion through a mechanism similar to that of sulfonylureas, although they generally result in less reduction in blood glucose than sulfonylureas. They have rapid action and have less tendency to cause hypoglycemia than sulfonylureas. Their use has been limited by high cost and lack of advantage over the sulfonylureas.

Thiazolidinediones

The thiazolidinediones (TZDs) activate the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ), which leads to changes in transcription rates of multiple genes. The net effect is reduced insulin resistance, and the resulting augmented actions of insulin lead to increased glucose uptake in peripheral tissues and reduced hepatic glucose production. Pioglitazone typically lowers HbA_{1c} by 0.5% to 1.4% and carries a low risk of hypoglycemia. Potential side effects include weight gain and hepatotoxicity.

Glucagon-Like Peptide-1 Analogues

Glucagon-like peptide-1 (GLP-1) is one of several hormones produced in the small intestine (designated *incretins*) that modify gastrointestinal motility and insulin secretion. The GLP-1 analogues, exenatide, liraglutide, and albiglutide, bind to GLP-1 receptors and improve blood glucose control by enhancing insulin-dependent insulin secretion, slowing gastric emptying, suppressing postprandial glucagon production, and decreasing food intake through enhanced satiety. This results in decreases in HbA_{1c} by 0.5% to 1.5% and modest weight loss (in the range of 3 kg). They are administered via injection with prefilled pens—exenatide twice daily or once weekly in long-acting form, liraglutide once daily, and albiglutide once weekly. The most common side effects are nausea and sometimes diarrhea, likely related to the drugs' effects on gastrointestinal motility. GLP-1 analogue use is tempered by the inconvenience of injection, relatively high cost, and a lack of long-term data on durability of weight loss or other outcome benefits. They most often are used as second-line agents in conjunction with other glucose-lowering drugs or insulin.

Dipeptidyl Peptidase-4 Inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors—sitagliptin, saxagliptin, linagliptin, and alogliptin—block the deactivation of GLP-1 (described in the previous section) and glucose-dependent insulinotropic peptide (GIP), peptide hormones that are important in the regulation of glucose homeostasis. Some of the effects of DPP-4 inhibitors may overlap with those of administered GLP-1 analogues, but they likely have additional actions by increasing levels of hormones other than GLP-1. DPP-4