daily, daily, and weekly injectable formulations, can be used as combination therapy with metformin, sulfonylureas, and thiazolidinediones. Some patients taking insulin secretagogues may require a reduction in those agents to prevent hypoglycemia. The major side effects are nausea, vomiting, and diarrhea. Some formulations carry a black box warning from the FDA because of an increased risk of thyroid C-cell tumors in rodents and are contraindicated in individuals with medullary carcinoma of the thyroid or multiple endocrine neoplasia. Because GLP-1 receptor agonists slow gastric emptying, they may influence the absorption of other drugs. Whether GLP-1 receptor agonists enhance beta cell survival, promote beta cell proliferation, or alter the natural history of type 2 DM is not known. Other GLP-1 receptor agonists and formulations are under development.

DPP-IV inhibitors inhibit degradation of native GLP-1 and thus enhance the incretin effect. DPP-IV, which is widely expressed on the cell surface of endothelial cells and some lymphocytes, degrades a wide range of peptides (not GLP-1 specific). DPP-IV inhibitors promote insulin secretion in the absence of hypoglycemia or weight gain and appear to have a preferential effect on postprandial blood glucose. The levels of GLP-1 action in the patient are greater with the GLP-1 receptor agonists than with DPP-IV inhibitors. DPP-IV inhibitors are used either alone or in combination with other oral agents in type 2 DM. Reduced doses should be given to patients with renal insufficiency. Initial concerns about the pancreatic side effects of GLP-1 receptor agonists and DPP-IV inhibitors (pancreatitis, possible premalignant lesions) appear to be unfounded.

α-GLUCOSIDASE INHIBITORS α-Glucosidase inhibitors reduce postprandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion (Table 418-5). Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes significantly to the hyperglycemic state in type 2 DM. These drugs, taken just before each meal, reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen. Therapy should be initiated at a low dose with the evening meal and increased to a maximal dose over weeks to months. The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligosaccharides to the large bowel and can be reduced somewhat by gradual upward dose titration. α-Glucosidase inhibitors may increase levels of sulfonylureas and increase the incidence of hypoglycemia. Simultaneous treatment with bile acid resins and antacids should be avoided. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2 mg/dL). This class of agents is not as potent as other oral agents in lowering the HbA_{1c} but is unique because it reduces the postprandial glucose rise even in individuals with type 1 DM. If hypoglycemia from other diabetes treatments occurs while taking these agents, the patient should consume glucose because the degradation and absorption of complex carbohydrates will be retarded.

THIAZOLIDINEDIONES Thiazolidinediones (Table 418-5) reduce insulin resistance by binding to the PPAR-γ (peroxisome proliferator–activated receptor γ) nuclear receptor (which forms a heterodimer with the retinoid X receptor). The PPAR-γ receptor is found at highest levels in adipocytes but is expressed at lower levels in many other tissues. Agonists of this receptor regulate a large number of genes, promote adipocyte differentiation, reduce hepatic fat accumulation, and promote fatty acid storage. Thiazolidinediones promote a redistribution of fat from central to peripheral locations. Circulating insulin levels decrease with use of the thiazolidinediones, indicating a reduction in insulin resistance. Although direct comparisons are not available, the two currently available thiazolidinediones appear to have similar efficacy. The prototype of this class of drugs, troglitazone, was withdrawn from the U.S. market after reports of hepatotoxicity and an association with an idiosyncratic liver reaction that sometimes led to hepatic failure. Although rosiglitazone and pioglitazone do not appear to induce the liver abnormalities seen with troglitazone, the FDA recommends measurement of liver function tests prior to initiating therapy.

Rosiglitazone raises low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides slightly. Pioglitazone raises HDL to a greater degree and LDL a lesser degree but lowers triglycerides. The clinical significance of the lipid changes with these agents is not known and may be difficult to ascertain because most patients with type 2 DM are also treated with a statin.

Thiazolidinediones are associated with weight gain (2–3 kg), a small reduction in the hematocrit, and a mild increase in plasma volume. Peripheral edema and CHF are more common in individuals treated with these agents. These agents are contraindicated in patients with liver disease or CHF (class III or IV). The FDA has issued an alert that rare patients taking these agents may experience a worsening of diabetic macular edema. An increased risk of fractures has been noted in women taking these agents. Thiazolidinediones have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome. Women should be warned about the risk of pregnancy because the safety of thiazolidinediones in pregnancy is not established.

Concerns about increased cardiovascular risk associated with rosiglitazone led to considerable restrictions on its use and to the FDA issuing a "black box" warning in 2007. However, based on new information, the FDA has revised its guidelines and categorizes rosiglitazone similar to other drugs for type 2 DM. Because of a possible increased risk of bladder cancer, pioglitazone is part of an ongoing FDA safety review.

Sodium-Glucose Co-Transporter 2 Inhibitors (SLGT2) These agents (Table 418-5) lower the blood glucose by selectively inhibiting this co-transporter, which is expressed almost exclusively in the proximal, convoluted tubule in the kidney. This inhibits glucose reabsorption, lowers the renal threshold for glucose, and leads to increased urinary glucose excretion. Thus, the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion. Because these agents are the newest class to treat type 2 DM (Table 418-5), clinical experience is limited. Due to the increased urinary glucose, urinary or vaginal infections are more common, and the diuretic effect can lead to reduced intravascular volume. As part of the FDA approval of canagliflozin in 2013, postmarketing studies for cardiovascular outcomes and for monitoring bladder and urinary cancer risk are under way.

OTHER THERAPIES FOR TYPE 2 DM

Bile acid–binding resins Evidence indicates that bile acids, by signaling through nuclear receptors, may have a role in metabolism. Bile acid metabolism is abnormal in type 2 DM. The bile acid–binding resin colesevelam has been approved for the treatment of type 2 DM (already approved for treatment of hypercholesterolemia). Because bile acid–binding resins are minimally absorbed into the systemic circulation, how bile acid–binding resins lower blood glucose is not known. The most common side effects are gastrointestinal (constipation, abdominal pain, and nausea). Bile acid–binding resins can increase plasma triglycerides and should be used cautiously in patients with a tendency for hypertriglyceridemia. The role of this class of drugs in the treatment of type 2 DM is not yet defined.

Bromocriptine A formulation of the dopamine receptor agonist bromocriptine (Cycloset) has been approved by the FDA for the treatment of type 2 DM. However, its role in the treatment of type 2 DM is uncertain.

INSULIN THERAPY IN TYPE 2 DM Insulin should be considered as the initial therapy in type 2 DM, particularly in lean individuals or those with severe weight loss, in individuals with underlying renal or hepatic disease that precludes oral glucose-lowering agents, or in individuals who are hospitalized or acutely ill. Insulin therapy is ultimately required by a substantial number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes. Both physician and patient reluctance often delay the initiation of insulin therapy, but glucose control and patient well-being are improved by insulin therapy in patients who have not reached the glycemic target.