TABLE 418-5 AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE 2 DIABETES

	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%)[b]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Oral						
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis	Serum creatinine >1.5 mg/dL (men) >1.4 mg/dL (women) (see text), CHF, radiographic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c**]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors[c***]	Prolong endogenous GLP-1 action	Alogliptin, Anagliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia		Reduced dose with renal disease; one associated with increase heart failure risk; possible association with ACE inhibitor–induced angioedema
Insulin secretagogues: Sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues: Nonsulfonylureas[c***]	↑ Insulin secretion	Nateglinide, repaglinide, mitiglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
Sodium-glucose cotransporter 2 inhibitors[***]	↑ Urinary glucose excretion	Canagliflozin, dapagliflozin, empagliflozin	0.5–1.0	Insulin secretion and action independent	Urinary and vaginal infections, dehydration, exacerbate tendency to hyperkalemia	Limited clinical experience; moderate renal insufficiency
Thiazolidinediones[c***]	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease
Parenteral						
Amylin agonists[c,d***]	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
GLP-1 receptor agonists[c***]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Exenatide, liraglutide, dulaglutide	0.5–1.0	Weight loss, do not cause hypoglycemia	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid
Insulin[c,d****]	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text and Table 418-4	Not limited	Known safety profile	Injection, weight gain, hypoglycemia	
Medical nutrition therapy and physical activity[c*]	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult, long-term success low	

[a]Examples are approved for use in at least one country, but may not be available in the United States or all countries. Examples may not include all agents in the class. [b]HbA*1c* reduction (absolute) depends partly on starting HbA_{1c}. [c]Used for treatment of type 2 diabetes. [d]Used in conjunction with insulin for treatment of type 1 diabetes. Cost of agent: *low, **moderate, ***high, ****variable.

Note: Some agents used to treat type 2 DM are not included in table (see text).

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CV, cardiovascular; GI, gastrointestinal; HbA_{1c}, hemoglobin A_{1c}.

INSULIN SECRETAGOGUES—AGENTS THAT ENHANCE GLP-1 RECEPTOR SIGNALING

"Incretins" amplify glucose-stimulated insulin secretion (Chap. 417). Agents that either act as a GLP-1 receptor agonist or enhance endogenous GLP-1 activity are approved for the treatment of type 2 DM (Table 418-5). Agents in this class do not cause hypoglycemia because of the glucose-dependent nature of incretin-stimulated insulin secretion (unless there is concomitant use of an agent that can lead to hypoglycemia—sulfonylureas, etc.). Exenatide, a synthetic version of a peptide initially identified in the saliva of the Gila monster (exendin-4), is an analogue of GLP-1. Unlike native GLP-1, which has a half-life of >5 min, differences in the exenatide amino acid sequence render it resistant to the enzyme that degrades GLP-1 (dipeptidyl peptidase IV [DPP-IV]). Thus, exenatide has prolonged GLP-1-like action and binds to GLP-1 receptors found in islets, the gastrointestinal tract, and the brain. Liraglutide, another GLP-1 receptor agonist, is almost identical to native GLP-1 except for an amino acid substitution and addition of a fatty acyl group (coupled with a γ-glutamic acid spacer) that promote binding to albumin and plasma proteins and prolong its half-life. GLP-1 receptor agonists increase glucose-stimulated insulin secretion, suppress glucagon, and slow gastric emptying. These agents do not promote weight gain; in fact, most patients experience modest weight loss and appetite suppression. Treatment with these agents should start at a low dose to minimize initial side effects (nausea being the limiting one). GLP-1 receptor agonists, available in twice