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Type 2 Diabetes: A Pharmacologic Update

A review of established and newer agents, as well as combination therapies, used to treat this prevalent condition.

ABSTRACT: Of the more than 30 million Americans who have diabetes mellitus, as many as 95% have type 2 diabetes. While interventions for type 2 diabetes include modifying diet and exercise, pharmacologic therapy is a mainstay in diabetes treatment. In recent years, with the addition of new medications and medication classifications, pharmacologic therapy for type 2 diabetes has changed dramatically. Nurses need to understand the many pharmacologic agents and combination therapies now in use. This article includes established as well as more recently introduced type 2 diabetes medications, as well as nursing implications regarding patient education and the monitoring of patients for adverse effects.

Keywords: antidiabetic drugs, combination therapy, diabetes drugs, hypoglycemic agents, noninsulin therapy, pharmacologic therapy, type 2 diabetes

In 2015, 30.3 million Americans—9.4% of the U.S. population—had diabetes mellitus, with type 2 diabetes accounting for 90% to 95% of all cases.[1] The prevalence of type 2 diabetes increases with age, though it is extremely high among adults of all ages and has been diagnosed in adolescents as well. In 2012, diabetes-related complications, which include kidney failure, neuropathy, amputations, blindness, and cardiovascular disease, represented an estimated total cost of $245 billion in the United States.[1] Diabetes is among the most common medical diagnoses of U.S. adult ED visits and hospitalizations. In 2015 it was the seventh leading cause of death.[1]

Of the nearly 4 billion prescriptions written in the United States in 2010, an estimated 165 million were for antidiabetic drugs, which ranked sixth among drug classifications prescribed that year.[2] As the number of type 2 diabetes diagnoses rises, prescriptions for antidiabetic drugs are expected to increase as well. In order to provide appropriate patient education and ensure safe, effective monitoring of patients receiving pharmacologic treatment for type 2 diabetes, nurses need to understand the mechanisms of action, adverse effects, and special considerations associated with both new as well as older pharmacologic agents. This article describes these agents and current combination therapies. Although a detailed discussion of insulin therapy, which is often required for effective diabetes treatment, is beyond the scope of this article, we note the new insulin combination therapies prescribed to treat type 2 diabetes.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes is characterized by elevated levels of fasting and postprandial blood glucose as well as glycated hemoglobin (HbA_{1c}). The inability of the body to effectively regulate blood glucose levels results from multiple factors, including genetic predispositions and alterations, environmental and dietary circumstances, and exercise patterns. A common finding in type 2 diabetes is a reduced number of pancreatic beta cells.[3] In addition, genetic predisposition may reduce the ability of beta cells to secrete sufficient amounts of insulin in response to high levels of blood glucose. It's estimated that more than 220 genes are associated with the risk of developing type 2 diabetes.[4] Research into the genetic alterations

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that may contribute to type 2 diabetes is relatively new but expanding.

The primary behavioral factors that influence type 2 diabetes development are physical inactivity and a dietary intake that promotes obesity. Diets characterized by high levels of saturated fats have been linked to obesity, beta cell dysfunction, insulin resistance, and glucose intolerance.[3]

Obesity often causes systemic inflammation, which has been associated with beta cell dysfunction.[3] The interaction of these factors produces insulin resistance in the body tissues and impairs the suppression of postprandial glucagon secretion.[5]

Insulin resistance, which can occur in a variety of tissues, including liver and muscle cells, may result from the inability of insulin to bind to its receptor on the cell or from a post-receptor-binding defect.[4] In obesity, insulin resistance develops long before altered glucose regulation is evident.[5]

LIFESTYLE MODIFICATION

According to the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), lifestyle modification is an essential part of managing type 2 diabetes.[6] Lifestyle management should include regular physical activity, nutritional therapy, behavioral support, smoking cessation, and weight control. Several well-conducted randomized controlled trials and large prospective cohort studies have found diet and exercise interventions to be effective in reducing the risk of developing type 2 diabetes.[7] Weight control may include pharmacologic or surgical therapy in some cases. Nevertheless, the use of pharmacologic antidiabetic therapy should not be delayed when lifestyle interventions alone are not effective in normalizing blood glucose.

MANAGEMENT GOALS

The primary marker used to assess the efficacy of type 2 diabetes management is HbA_{1c}, which may be used to guide pharmacologic therapy. The AACE/ACE recommends an HbA_{1c} level of 6.5% or lower, if it can be safely and affordably maintained. Such factors as the patient's age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia, and motivation and adherence should be considered, with the understanding that management goals may change over time and that higher HbA_{1c} levels may be more appropriate for some patients.[6]

NONINSULIN PHARMACOLOGIC THERAPY

Biguanides: metformin. The only biguanide approved for use in the United States is metformin. Recommended by the American College of Physicians

Table 1. Drug Classes Commonly Used in the Treatment of Type 2 Diabetes

Drug Class	Site of Action	Examples	Mechanism of Action	Nursing Implications
α-glucosidase inhibitors	Intestine	• acarbose (Precose) • miglitol (Glyset)	• Delays carbohydrate digestion • Blocks starches	• Should be taken with first bite of a meal. • Do not give to patients with bowel disorders. • Monitor renal function. • Do not use in pregnancy. • Monitor serum digoxin levels, which may decrease.
Biguanides	Liver, muscles, intestine	• metformin (Glucophage, Glucophage XR, Glumetza, Fortamet)	• Decreases intestinal absorption of glucose • Increases glucose use in muscles • Decreases hepatic glucose production	• Stop use 48 hours before and for 48 hours after procedures requiring iodinated contrast media, resuming only when renal function has returned to baseline. • Advise patient that weight loss may occur. • Monitor renal function. • Monitor patient for lactic acidosis. • Monitor patient for vitamin B_{12} deficiency anemia.
DDP-4 inhibitors	Intestine	• alogliptin (Nesina) • linagliptin (Tradjenta) • saxagliptin (Onglyza) • sitagliptin (Januvia)	• Delays breakdown of incretin hormones • Stimulates increase in insulin release	• Can be taken with or without food. • Monitor renal function, adjusting dosage as needed. • Assess patient for angioedema if also taking an ACE inhibitor.
GLP-1 receptor agonists	Pancreas, stomach	• albiglutide (Tanzeum) • dulaglutide (Trulicity) • exenatide (Byetta, Bydureon) • liraglutide (Victoza, Saxenda) • lixisenatide (Adlyxin) • semaglutide (Ozempic)	• Stimulates insulin release • Decreases glucagon secretion • Slows gastric emptying	• Administered by subcutaneous injection twice daily, 30 minutes before meals. • Extended release is administered by subcutaneous injection weekly. • Should be administered in the thigh, abdomen, or upper arm. • Do not give to patients with severe GI disease, such as ulcerative colitis or Crohn's disease. • Advise patients that treatment is associated with increased risk of thyroid tumors. • Advise patients taking warfarin that risk of bleeding may increase; monitor INR.
Human amylin analogue	Stomach, liver	• pramlintide (Symlin)	• Slows gastric emptying • Decreases postprandial glucagon secretion	• Should be administered by subcutaneous injection immediately before meals. • Owing to variability of absorption, should be administered only in the thigh or abdomen, not the upper arm. • Monitor patient for increased risk of hypoglycemia if used with insulin.

Table 1. Continued

Meglitinides	Pancreas	• nateglinide (Starlix) • repaglinide (Prandin)	• Stimulates pancreatic secretion of insulin	• Should be taken with meals to prevent hypoglycemia. • Patient should monitor postprandial blood glucose. • Monitor liver function tests.
Second-generation sulfonylureas	Pancreas	• glimepiride (Amaryl) • glipizide (Glucotrol, Glucotrol XL) • glyburide (Diabeta, Glynase)	• Increases insulin secretion • Increases insulin sensitivity	• Advise patient of hypoglycemia risk. • All except glipizide should be taken with food; glipizide should be taken 30 minutes before a meal. • Older adults may require lower doses. • Monitor patient for reduced RBC, WBC, and platelets. • Monitor liver function tests. • Advise patients that treatment may cause photosensitivity.
SGLT-2 inhibitors	Kidney	• canagliflozin (Invokana) • dapagliflozin (Farxiga) • empagliflozin (Jardiance) • ertugliflozin (Steglatro)	• Lowers renal glucose threshold • Increases glycosuria	• Should be taken once daily, in the morning before first meal. • Monitor patient for genital or urinary tract infections. • Patients are at increased risk for amputation, which is particularly associated with canagliflozin, and should be monitored for PVD. • Monitor kidney function.
Thiazolidine-diones	Muscles, liver	• pioglitazone (Actos) • rosiglitazone (Avandia)	• Decreases insulin resistance • Increases glucose uptake muscles • Decreases hepatic glucose formation	• Should be taken once daily in the morning. • Monitor liver function tests. • Assess patients for symptoms of CHF. • Advise female patients of the risk of developing polycystic ovarian syndrome. • Advise female patients using hormonal birth control that the dosage may need to be increased.

ACE = angiotensin-converting enzyme; DDP-4 = dipeptidyl peptidase 4; CHF = congestive heart failure; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; INR = international normalized ratio; PVD = peripheral vascular disease; RBC = red blood cells; SGLT-2 = sodium–glucose cotransporter 2; WBC = white blood cells.

and the AACE/ACE as first-line pharmacologic treatment for type 2 diabetes when nonpharmacologic therapy does not adequately reduce HbA_{1c} levels, metformin was approved by the U.S. Food and Drug Administration (FDA) in 1995.[6,8] Metformin continues to be used to control blood glucose and to reduce the risk of cardiovascular complications, particularly in overweight and obese patients. In the landmark 1998 UK Prospective Diabetes Study, risk of stroke, myocardial infarction, and mortality were significantly reduced in patients allocated to metformin treatment.[9] Metformin, which is not associated with weight gain, has a strong safety profile, few adverse effects, good tolerability, and is the least expensive of the antidiabetic drugs used to treat type 2 diabetes.[10-13]

Mechanism of action. Metformin works in the liver to inhibit gluconeogenesis and glycogenolysis, which reduces hepatic glucose output.[10] It also improves insulin sensitivity in the tissues.[14] Because metformin does not stimulate pancreatic secretion of insulin, it is not associated with hypoglycemia, a common adverse effect of other antidiabetic drugs.[10]

Adverse effects. Metformin has few adverse effects; these may include nausea, anorexia, abdominal cramps, bloating, and diarrhea, all of which are generally mild and transient. The most serious, though rare, adverse effect associated with metformin is lactic acidosis. Risk of metformin-associated lactic acidosis is elevated in patients with renal impairment and with the use of contrast media.[10]

Special considerations. Metformin is associated with vitamin B_{12} deficiency, possibly because it may interfere with absorption of vitamin B_{12} in the distal ileum.[10, 15] For this reason, serum vitamin B_{12} should be monitored in patients with anemia or peripheral diabetic neuropathy. Since the use of iodine-containing contrast agents may cause renal failure in patients treated with metformin, patients scheduled for procedures that involve iodinated contrast media should be advised to suspend metformin usage 48 hours before such procedures and to resume metformin treatment no earlier than 48 hours following the procedures, after renal function is confirmed to have returned to baseline.[10]

Table 2. Adverse Effects Associated with Antidiabetic Drug Classes

Drug Class	Adverse Effects
α-glucosidase inhibitors	• Flatulence, bloating, diarrhea, abdominal pain
Biguanides	• Diarrhea, nausea, anorexia, abdominal cramps, bloating • Vitamin B_{12} deficiency anemia • Lactic acidosis (rare)
DPP-4 inhibitors	• Abdominal pain, cramping, nausea, vomiting, diarrhea • Headache • Skin reactions
GLP-1 receptor agonists	• Nausea (transient), vomiting, diarrhea, indigestion • Hypoglycemia • Headache, dizziness • Injection site reactions
Human amylin analogue	• Nausea, vomiting, anorexia • Headache • Injection site reactions
Meglitinides	• Hypoglycemia (common) • Headache • Weight gain
Second-generation sulfonylureas	• Hypoglycemia (very common) • Nausea, vomiting, gas • Weight gain • Skin rashes • Photosensitivity
SGLT-2 inhibitors	• Elevated risk of urinary tract infections • Increased urination • Genital mycotic infections • Increased risk of amputations • Hypovolemia with hypotension or dizziness (owing to increased osmotic diuresis)
Thiazolidinediones	• Weight gain, edema • Chest pain, dyspnea • Infections (urinary tract and upper respiratory tract) • Blurred vision • Increased risk of fracture

DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium–glucose cotransporter 2.

Additional medications. When metformin monotherapy is insufficient, additional agents may be added to achieve glycemic control. Over the past several years, many new classes of drugs, including injectable noninsulin drugs and injectable insulin combinations, have been approved for use in type 2 diabetes. Before selecting any additional medications, the prescriber and patient should discuss costs, insurance coverage, potential benefits, and adverse effects.[6, 8]

Second-generation sulfonylureas: glimepiride, glipizide, and glyburide. One of the oldest and, after metformin, least expensive categories of noninsulin antidiabetic agents,[11] sulfonylureas have been used for the management of type 2 diabetes for more than 50 years. Second-generation sulfonylureas are prescribed as a second-line or adjunctive treatment for type 2 diabetes when patients are unable to achieve target HbA_{1c} goals with metformin monotherapy. The second-generation sulfonylureas are preferred to the first-generation sulfonylureas (chlorpropamide, tolazamide, and tolbutamide) because they are more potent, carry a lower risk of hypoglycemia, and have both a more rapid onset of action and a shorter half-life.[16]

Mechanism of action. Known as insulin secretagogues, sulfonylureas inhibit the ATP-sensitive potassium channel of the pancreatic beta cells, stimulating pancreatic insulin release and enhancing peripheral insulin sensitivity.[17] As pancreatic beta cell function declines with disease progression, sulfonylureas become less effective.[11] Since some degree of pancreatic beta cell function is necessary for sulfonylureas to be effective, they are usually prescribed during the early stages of type 2 diabetes.

Adverse effects. Second-generation sulfonylureas are relatively potent in their ability to lower HbA_{1c} levels, but because they work to stimulate endogenous insulin release, they are associated with the greatest risk of hypoglycemia among noninsulin antidiabetic agents.[6] Sulfonylureas are also associated with a higher risk of cardiovascular mortality than metformin.[18] In addition, second-generation sulfonylureas are associated with such adverse effects as weight gain, gastrointestinal disturbance, and skin rashes.[6, 17]

Special considerations. All second-generation sulfonylureas are available as generic formulations, contributing to their relatively low cost and wide use. Most of these drugs should be taken with meals once a day or twice daily in divided doses; the exception is glipizide, which should be taken on an empty stomach 30 minutes before a meal.[19] Dosages may need to be adjusted in patients with renal insufficiency.[19, 20]

Meglitinides (glinides): nateglinide and repaglinide. Meglitinides are a selective class of insulin secretagogues that have a more rapid onset but shorter duration of action than the sulfonylureas. The use of meglitinides is limited owing to their frequent dosing.

Mechanism of action. Like sulfonylureas, meglitinides alter the ATP-sensitive potassium channel of the pancreatic beta cells, stimulating pancreatic insulin release. Taken primarily with meals, meglitinides are best suited for managing postprandial glucose elevations or sudden spikes in blood glucose levels.[17] Meglitinides are less effective than sulfonylureas in lowering HbA_{1c} levels, but they carry a lower risk of prolonged hypoglycemia.[6]

Adverse effects. The adverse effects most commonly reported with meglitinide use are hypoglycemia and weight gain.[21]

Special considerations. Because of their rapid onset, meglitinides should be taken with meals.[17] Patients should be advised to monitor blood glucose levels following meals. Meglitinides are primarily metabolized by the cytochrome P-450 enzyme system, and patients taking these drugs should have their liver function monitored.[22,23] Since this drug class is related to the sulfonylureas, patients who do not respond to sulfonylureas typically will not respond to meglitinides.

Thiazolidinediones (glitazones): pioglitazone and rosiglitazone. The thiazolidinediones are effective in reducing HbA_{1c} levels, provide stable glycemic control, and are associated with a low risk of hypoglycemia.[6]

Mechanism of action. Thiazolidinediones are the only antidiabetic agents that directly increase insulin sensitivity in muscle, fat, and liver tissues.[11,14] The thiazolidinediones are metabolized in the liver.[11] Since they do not stimulate insulin secretion, when taken alone they do not cause hypoglycemia.[14]

Adverse effects. In 2011, the FDA advised against the use of pioglitazone in patients with active bladder cancer or a history of bladder cancer.[24] Thiazolidinediones are also associated with elevated risk of bone fracture in women and should not be used by women with osteoporosis or osteopenia.[11] Because thiazolidinediones are associated with weight gain and edema, they are contraindicated in patients with New York Heart Association class III or IV heart failure.[11,21]

Special considerations. The thiazolidinediones are taken once daily in the morning. Premenopausal female patients using hormonal contraception should be advised that thiazolidinediones may reduce serum levels of ethinyl estradiol and norethindrone, causing ovulation and increasing the risk of pregnancy. All premenopausal women treated with a thiazolidinediones should speak with their contraceptive prescriber about increasing their hormonal contraceptive dosage or using an alternative form of contraception.[25,26]

Table 3. Combination Antidiabetic Medications

Trade Name	Combination Drug
Combinations with metformin	
Actoplus Met, Actoplus Met XR	pioglitazone
Avandamet[a]	rosiglitazone
Glucovance[a]	glyburide
Invokamet, Invokamet XR	canagliflozin
Janumet, Janumet XR	sitagliptin
Jentadueto, Jentadueto XR	linagliptin
Kazano	alogliptin
Kombiglyze XR	saxagliptin
Metaglip[a]	glipizide
Prandimet[a]	repaglinide
Segluromet	ertugliflozin
Synjardy, Synjardy XR	empagliflozin
Xigduo XR	dapagliflozin
Combinations with insulin (injection)	
Soliqua 100/33	insulin glargine–lixisenatide
Xultophy 100/3.6	insulin degludec–liraglutide
Other combinations	
Avandaryl[a]	glimepiride–rosiglitazone
Duetact	glimepiride–pioglitazone
Glyxambi	empagliflozin–linagliptin
Oseni	alogliptin–pioglitazone
Qtern	dapagliflozin–saxagliptin
Steglujan	ertugliflozin–sitagliptin

[a]This drug is available as a generic combination; the brand name has been discontinued.

The α-glucosidase inhibitors: acarbose and miglitol. The only α-glucosidase inhibitors approved for use in the United States are acarbose and miglitol. The α-glucosidase inhibitors can be used as monotherapy or in combination with metformin.[6]

Mechanism of action. The α-glucosidase inhibitors work by impeding the conversion of oligosaccharides to monosaccharides.[21] As a result, carbohydrate absorption in the intestine is delayed and blood glucose levels are stabilized.

Adverse effects. The α-glucosidase inhibitors are less effective than metformin and the sulfonylureas in lowering HbA_{1c} levels, but they carry a low risk of hypoglycemia unless used with a sulfonylurea or insulin therapy.[21] Adverse effects include bloating, flatulence, and diarrhea.[6]

Special considerations. The α-glucosidase inhibitors are taken three times a day with meals. Because the drugs work in the intestine, they are contraindicated in patients with any type of bowel disorder.[27,28] In patients taking these drugs, hypoglycemia should be reversed with a glucose, rather than a sucrose, source.[11] Creatinine clearance should be monitored.[11]

Dipeptidyl peptidase 4 (DPP-4) inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin. The first drug classified as a DPP-4 inhibitor was sitagliptin, which received FDA approval in 2006.[29] DPP-4 inhibitors may be used as initial monotherapy when metformin, sulfonylureas, or thiazolidinediones are not well tolerated or are contraindicated.[6] DPP-4 inhibitors are also commonly added to metformin in patients who do not meet their treatment goal after three months of metformin monotherapy.

Mechanism of action. These drugs reduce the effects of the enzyme DPP-4, which metabolizes the incretin hormones that are released into the bloodstream from the gastrointestinal system in the presence of food. The incretin hormones are responsible for at least 50% of the insulin secreted following glucose ingestion.[30] By inhibiting incretin metabolism, the DPP-4 inhibitors stimulate insulin secretion, thereby reducing blood glucose levels.[6]

Sitagliptin, the oldest of the DPP-4 inhibitors, has been studied extensively in clinical trials, and has proven effective in reducing HbA_{1c}, fasting plasma glucose, and two-hour postprandial glucose levels when used as monotherapy or in combination with other antidiabetic agents.[31] The Comparative Outcomes Study of Metformin Intervention Versus Conventional (COSMIC) Approach demonstrated a continued glucose-lowering effect of combination therapy with sitagliptin and metformin for up to four years in patients with type 2 diabetes.[29]

Adverse effects. Sitagliptin is associated with constipation, and the prescribing information warns that there have been postmarketing reports of acute pancreatitis associated with the use of all DPP-4 inhibitors. There have been no demonstrated effects of DPP-4 inhibitors on body weight.[32-35]

Special considerations. DPP-4 inhibitors are taken once daily, with or without meals. Since linagliptin is primarily eliminated in feces, with only about 5% excreted by the kidneys, it may be used instead of other drugs in this class by patients with renal impairment.[36]

Glucagon-like peptide 1 (GLP-1) receptor agonists: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide. The GLP-1 receptor agonists are administered by subcutaneous injection. The first of these drugs, exenatide, was approved by the FDA in 2005. Although GLP-1 receptor agonists are often used with metformin when treatment goals are not achieved with metformin monotherapy, like the DPP-4 inhibitors they may also be used as initial monotherapy.[6] In addition to their glucose-lowering effects, GLP-1 receptor agonists also promote weight loss, though liraglutide is the only drug in this class that is FDA approved for treating obesity.[37] The dosing for obesity is higher than that for glycemic control.

Mechanism of action. GLP-1 is an incretin secreted by the intestinal mucosa. By stimulating the GLP-1 receptor, these drugs promote the release of insulin from the pancreas, which lowers blood glucose levels. GLP-1 receptor agonists also suppress glucagon secretion and slow gastric emptying.[38]

Adverse effects. GLP-1 receptor agonists are associated with nausea, vomiting, constipation, and diarrhea. The risk of hypoglycemia with the use of exenatide is low. There is a risk of injection site reactions for these medications. Clinical trials have reported thyroid neoplasms, elevated calcitonin levels, and goiters in patients treated with liraglutide.[39] Nasopharyngitis was reported in an albiglutide efficacy and tolerability study, but the incidence was similar to that in the placebo group.[40]

In addition to their glucose-lowering effects, GLP-1 receptor agonists also promote weight loss, though liraglutide is the only drug in this class that is FDA approved for treating obesity.

Special considerations. Liraglutide may be administered any time of day, independent of meals, but is typically administered in the morning, once daily. Albiglutide, a long-acting agent, is administered once weekly.[40] Instruct patients to inject the medication into the thigh, upper arm, or abdomen and to rotate injection sites.

Sodium–glucose cotransporter 2 (SGLT-2) inhibitors: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. The newest of the drugs used to treat type 2 diabetes are the SGLT-2 inhibitors. The first of these drugs received FDA approval in 2013. The SGLT-2 inhibitors are indicated as monotherapy for patients in whom metformin is contraindicated or not tolerated and as combination therapy with metformin

or other antidiabetic agents to help patients achieve their goals. These drugs have demonstrated efficacy in significantly reducing HbA_{1c} levels, both as monotherapy and in combination with metformin.[41]

Mechanism of action. SGLT-2 is responsible for filtering glucose reabsorption in the proximal tubules of the kidney.[42] By inhibiting this action, SGLT-2 inhibitors increase urinary excretion of glucose, thereby reducing serum glucose levels.

Adverse effects. When SGLT-2 inhibitors are used in combination with other antidiabetic agents, hypoglycemia may occur. The loss of glucose in the urine may produce osmotic diuresis triggering hypovolemia, postural hypotension, and dizziness. More significant adverse reactions include urinary tract infections, genital mycotic infections (more common in women than men), and an increased risk of amputations, which is particularly associated with canagliflozin and more likely in patients with a history of peripheral vascular disease or prior amputation.[42,43] Canagliflozin is also associated with an increased risk of fracture and should be used cautiously in women.[44]

Special considerations. The SGLT-2 inhibitors are taken once a day in the morning, with or without food. They are contraindicated in patients with renal disease.

Human amylin analogue: pramlintide. Approved by the FDA in 2005, pramlintide has been shown to improve HbA_{1c} levels by 0.2% to 0.4%.[45]

Mechanism of action. Amylin is a 37-amino acid peptide that is secreted by pancreatic beta cells in response to the ingestion of starches. It reduces blood glucose levels by slowing gastric emptying, thereby delaying the absorption of carbohydrates, blocking the secretion of glucagon, and enhancing the feeling of fullness, thus limiting the intake of additional carbohydrates. People with type 2 diabetes are often deficient in amylin.[46]

Adverse effects. Pramlintide is associated with nausea, vomiting, and a diminished appetite.

Special considerations. Pramlintide is injected subcutaneously before meals that contain 250 or more calories or 30 or more grams of carbohydrates.[46] This medication should be injected into the thigh or abdomen. The upper arm should not be used for injection owing to the variability of absorption. Pramlintide should not be used in patients with gastroparesis.

An overview of antidiabetic drug classes, their sites and mechanisms of action, and nursing implications are presented in Table 1; associated adverse effects can be found in Table 2.

COMBINATION THERAPY

If patients are not meeting treatment goals with metformin or other monotherapy, additional drugs or combination therapies, some with extended-release formulations, are typically prescribed (see Table 3). Nurses need to familiarize themselves with these combinations to provide effective patient education and continued assessment. ▼

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REFERENCES

1. Centers for Disease Control and Prevention. *National diabetes statistics report, 2017. Estimates of diabetes and its burden in the United States*. Atlanta; 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.
2. Stone K. *The number one prescribed medications by drug class*. 2018. https://www.thebalance.com/the-most-prescribed-medications-by-drug-class-2663215.
3. Kahn SE, et al. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2014;383(9922):1068-83.
4. Surampudi PN, et al. Emerging concepts in the pathophysiology of type 2 diabetes mellitus. *Mt Sinai J Med* 2009;76(3):216-26.
5. Carrera Boada CA, Martínez-Moreno JM. Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit." *Nutr Hosp* 2013;28 Suppl 2:78-87.
6. Garber AJ, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2018 executive summary. *Endocr Pract* 2018;24(1):91-120.
7. Mutie PM, et al. Lifestyle precision medicine: the next generation in type 2 diabetes prevention? *BMC Med* 2017;15(1):171.
8. Qaseem A, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med* 2017;166(4):279-90.
9. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352(9131):854-65.
10. Apampa B. Pharmacology and safe prescribing of metformin. *NursePrescribing* 2012;10(12):597-602.
11. George CM, et al. Management of blood glucose with noninsulin therapies in type 2 diabetes. *Am Fam Physician* 2015;92(1):27-34.
12. Inzucchi SE. Is it time to change the type 2 diabetes treatment paradigm? No! Metformin should remain the foundation therapy for type 2 diabetes. *Diabetes Care* 2017;40(8):1128-32.
13. Yandrapalli S, et al. Cardiovascular benefits and safety of non-insulin medications used in the treatment of type 2 diabetes mellitus. *Postgrad Med* 2017;129(8):811-21.
14. Johnson T. Pharmcology of diabetes drugs: a perspective for dental hygienists. *Access: the Newsmagazine of the American Dental Hygienists' Association* 2010;24(6):14-23.
15. Wooley AC, Kerr JL. Monitoring patients on metformin: recent changes and rationales. *J Pharm Technol* 2018;34(1):28-36.
16. Chaudhury A, et al. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. *Front Endocrinol (Lausanne)* 2017;8:6.

17. Laight D. The pharmacology of oral antidiabetic agents. *NursePrescribing* 2014;12(12):604-7.
18. Maruthur NM, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2016; 164(11):740-51.
19. Pfizer. *Prescribing information: Glucotrol (glipizide) tablet*. New York, NY; 2008 Sep. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017783s019lbl.pdf.
20. Sanofi-Aventis. *Prescribing information: Amaryl (glimepiride) tablets*. Bridgewater, NJ; 2013 Oct. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020496s027lbl.pdf.
21. Lew KN, Wick A. Pharmacotherapy of type 2 diabetes mellitus: navigating current and new therapies. *Medsurg Nurs* 2015;24(6):413-9, 438.
22. Novartis Pharmaceuticals Corporation. *Prescribing information: Starlix (nateglinide) tablets*. East Hanover, NJ; 2008 Jul. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021204s011lbl.pdf.
23. Novo Nordisk A/S. *Prescribing information: Prandin (repaglinide) tablets (0.5, 1, and 2 mg)*. Princeton, NJ; 2008 Jul. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020741s035lbl.pdf.
24. U.S. Food and Drug Administration. *Updated FDA review concludes that the use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer*. Silver Spring, MD; 2016 Dec 12. FDA drug safety communication; https://www.fda.gov/Drugs/DrugSafety/ucm519616.htm.
25. Takeda Pharmaceuticals. *Prescribing information: Actos (pioglitazone hydrochloride) tablets for oral use*. Deerfield, IL; 2011 Jul. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf.
26. Woo TM, Robinsion MV. *Pharmacotherapeutics for advanced practice nurse prescribers*. 4th ed. Philadelphia: F.A. Davis Company; 2015.
27. Bayer HealthCare Pharmaceuticals. *Prescribing information: Precose (acarbose tablets)*. Wayne, NJ; 2011 Nov. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020482s025lbl.pdf.
28. Pfizer. *Prescribing information: Glyset (miglitol) tablets for oral use*. New York, NY; 2012 Aug. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020682s010lbl.pdf.
29. Ku EJ, et al. Four-year durability of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes in clinical practice; COSMIC study. *PLoS One* 2015; 10(6):e0129477.
30. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev* 2008;60(4):470-512.
31. Plosker GL. Sitagliptin: a review of its use in patients with type 2 diabetes mellitus. *Drugs* 2014;74(2):223-42.
32. AstraZeneca Pharmaceuticals. *Prescribing information: Onglyza (saxagliptin) tablets, for oral use*. Wilmington, DE; 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022350s014lbl.pdf.
33. Boehringer Ingelheim Pharmaceuticals. *Prescribing information: Tradjenta (linagliptin) tablets*. Ridgefield, CT; 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/201280s005lbl.pdf.
34. Merck and Company, Inc. *Prescribing information: Januvia (sitagliptin) tablets*. Whitehorse Station, NJ; 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s019lbl.pdf.
35. Takeda Pharmaceuticals. *Prescribing information: Nesina (alogliptin) tablets*. Deerfield, IL; 2013 Jan. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf.
36. McKeage K. Linagliptin: an update of its use in patients with type 2 diabetes mellitus. *Drugs* 2014;74(16):1927-46.
37. Isaacs D, et al. Role of glucagon-like peptide 1 receptor agonists in management of obesity. *Am J Health Syst Pharm* 2016; 73(19):1493-507.
38. McCormack PL. Exenatide twice daily: a review of its use in the management of patients with type 2 diabetes mellitus. *Drugs* 2014;74(3):325-51.
39. Peterson GE, Pollom RD. Liraglutide in clinical practice: dosing, safety and efficacy. *Int J Clin Pract Suppl* 2010(167): 35-43.
40. Davis PN, et al. Albiglutide: a once-weekly glucagon-like peptide-1 receptor agonist for type 2 diabetes mellitus. *Am J Health Syst Pharm* 2015;72(13):1097-103.
41. Miller EM. Elements for success in managing type 2 diabetes with SGLT-2 inhibitors: overview of the efficacy and safety of SGLT-2 inhibitors in type 2 diabetes mellitus. *J Fam Pract* 2017; 66(2 Suppl):S5-S12.
42. Dixit D, et al. Empagliflozin: a sodium-glucose cotransporter 2 inhibitor for treatment of type 2 diabetes. *Am J Health Syst Pharm* 2015;72(22):1943-54.
43. Filippas-Ntekouan S, et al. SGLT2 inhibitors: are they safe? *Postgrad Med* 2018;130(1):72-82.
44. Wolverton D, Blair MM. Fracture risk associated with common medications used in treating type 2 diabetes mellitus. *Am J Health Syst Pharm* 2017;74(15):1143-51.
45. Lee NJ, et al. Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. *Ann Fam Med* 2010;8(6): 542-9.
46. Edelman S, et al. Pramlintide in the treatment of diabetes mellitus. *BioDrugs* 2008;22(6):375-86.

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