continuing education for pharmacists

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2016 AACE/ACE Guidelines on Type 2 Diabetes Management and New Glycemic Control Agents

Amanda R. Kriesen, R.Ph., PharmD, and Erin Bastick, R.Ph., PharmD

Drs. Amanda Kriesen and Erin Bastick have no relevant financial relationships to disclose.

Goal. The goals of this lesson are to provide an overview of the 2016 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) consensus statement regarding the management of hyperglycemia associated with type II diabetes, and to discuss empagliflozin/metformin (Synjardy®), insulin degludec (Tresiba®), insulin degludec/insulin aspart (Ryzodeg 70/30®), insulin glargine (Basaglar®) and lixisenatide (Adlyxin®).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize the 2016 AACE/ACE consensus statement regarding treatment of hyperglycemia associated with diabetes mellitus;
2. list lifestyle modifications that contribute to improved glycemic control;
3. demonstrate an understanding of various classes of antihyperglycemic agents;
4. recognize the mechanism of action of the new antihyperglycemic agents and their respective roles in treating diabetes; and
5. identify pertinent prescribing and counseling points associated with the new drugs.

Background

Diabetes mellitus is a chronic condition caused by endogenous insulin impairment, which leads to subsequent increased blood glucose. It is a principal cause of morbidity and mortality worldwide. Type I diabetes (T1D) is characterized by a lack of insulin production, whereas type II diabetes (T2D) is characterized by the body's ineffective use of endogenous insulin.

In 2014, an estimated 29.1 million Americans had diabetes; with approximately one in four of these Americans unknowingly suffering from the condition. The implications of serious health complications arising from diabetes are extensive. Comorbidities such as blindness, renal failure, heart disease, stroke, and neuropathy significantly increase healthcare expenditures and reduce quality of life. Diabetes is associated with a high incidence of depression, and adversely impacts employment with increased absenteeism, and decreased productivity. Furthermore, individuals with diabetes are at a 50 percent higher risk of death than those without diabetes.

Due to the increasing frequency of T2D diagnoses in the general population, pharmacists are in a unique position to help guide patients with diabetes. Pharmacists' in-depth knowledge of various antihyperglycemic medication profiles, proficient communication skills, and accessibility in the community allow opportunities for effective patient communication and education. Furthermore, community pharmacists who see patients with diabetes on a regular basis may be able to assist in evaluating efficacy of pharmacologic therapy and effectively communicating results and/or drug therapy-related concerns with prescribers. An interdisciplinary approach to patient care is a vital component of comprehensive care.

Overview of 2016 AACE/ACE Type II Diabetes Management Algorithm

Founding principles of the AACE/ACE type II diabetes algorithm include recommendations pertaining to lifestyle optimization, patient-specific pharmacologic therapy, combination therapy, and medication therapy for comorbid disease states commonly associated with T2D. It is important to note that the AACE/ACE guidelines are not the only set of diabetes guidelines available. The American Diabetes Association (ADA) has also published guidelines. For the purposes of this lesson, only the AACE/ACE guidelines will be reviewed.

Both genetic and environmental factors contribute to development of T2D. Physical inactivity, excessive weight gain, and obesity are all contributors to endogenous insulin resistance. Lifestyle modifications such as medical nutrition therapy, regular physical activity, sufficient sleep, and avoidance of all tobacco products are key components in management of T2D. Medical nutrition therapy involves a specifically tailored diet that is designed and monitored by a registered dietitian or a professional nutritionist. An optimal weight should be attained and maintained by a primarily plant-based diet

Table 1
Goals for glycemic control in nonpregnant adults with diabetes

Hemoglobin A1C Patients without concurrent serious illness and low hypoglycemic risk (e.g., recent-onset T2D, no clinically significant cardiovascular disease)	≤6.5 percent
Patients with concurrent serious illness and high hypoglycemic risk (e.g., history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing T2D with inability to attain target A1C)	>6.5-8.0 percent
Preprandial capillary plasma glucose	80-130 mg/dL
Peak postprandial capillary plasma glucose (1-2 hours after beginning of meal)	<180 mg/dL

high in polyunsaturated and monounsaturated fats, limiting intake of saturated fatty acid, and avoidance of trans fats. Physical activity, both aerobic and strength-training, has been shown to improve glycemic control, lipid levels, and blood pressure. Patients should be advised to engage in at least 150 minutes per week of moderate physical activity. Sleep deprivation is known to aggravate insulin resistance, hypertension, hyperglycemia, and dyslipidemia. Patients should be advised to sleep approximately seven hours per night, as adequate rest is imperative in maintaining energy levels and well-being. Lastly, patients should be advised to avoid use of all tobacco products. Structured smoking cessation programs are recommended for patients unable to quit on their own.

Goals for Glycemic Control

In patients with T2D, achieving the hemoglobin A1C (A1C) goal and glucose target require a multifactorial approach which balances age, comorbid disease states, and hypoglycemia risk. Hemoglobin A1C is a measurement of how much glucose binds to circulating hemoglobin in the blood; it serves as a reflection of glycemic control over the past six to eight weeks. A glucose target, in contrast, is a measurement which reflects a patient's blood glucose concentration at one particular point in time. AACE/ACE supports an A1C goal of ≤6.5 percent for most patients; however, A1Cs up to 8 percent are often upheld if the ideal target cannot be reached without adverse outcomes. A preprandial capillary plasma glucose of 80 to 130 mg/dL and a postprandial capillary plasma glucose of <180 mg/dL may further aid in reducing A1C. Again, treatment goals should be tailored per individual patient needs and demographics. Several clinical studies have published evidence supporting individualization of glycemic targets. Table 1 provides an overview of glycemic control goals for nonpregnant adults with diabetes.

Pharmacotherapy

The 2016 AACE/ACE algorithm provides an aid in selecting therapy. In the algorithm, antihyperglycemic drug classes are listed in order of preference. Several classes of antihyperglycemic agents exist; however, therapeutic selection should be individualized. Classes include biguanides, glucagon-like peptide-1 (GLP-1) agonists (incretin mimetics), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), bile acid sequestrants, alpha-glucosidase inhibitors, sulfonylureas, and dopamine receptor agonists. Interventions should integrate patient-specific dynamics such as socioeconomic status, health literacy, comorbid disease states, tolerability, and affordability. In addition to selecting therapy specific to patient dynamics, creating an individualized medication regimen may further encourage compliance.

The AACE/ACE algorithm recommends a combination of lifestyle therapy plus antihyperglycemic monotherapy (preferably metformin) in newly-diagnosed diabetes or mild hyperglycemia (A1C <7.5 percent). Metformin should remain the cornerstone of all antihyperglycemic pharmacotherapy, if not contraindicated. Acceptable alternatives to metformin monotherapy include GLP-1 agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and TZDs. Combination therapy is considered in patients unable to attain glycemic targets after three months of monotherapy or patients presenting with A1C >7.5 percent. Dual therapy often includes metformin plus a GLP-1 agonist, SGLT-2 inhibitor, DPP-4 inhibitor, or a TZD. Patients intolerant to metformin should be given dual therapy with two medications from other classes that have complementary mechanisms of action. If dual therapy fails to provide appropriate glycemic targets, the addition of a third agent may be considered. It is important to note, however, that any third-line agent may be less effective in comparison to the same medication when used as first- or second-line therapy. Patients with A1C >9 percent receive greater benefit from insulin; however, in the absence of significant symptoms, these patients may be initiated on maximum doses of combination therapy.

Biguanides. Metformin is considered first-line therapy in treating T2D. The sole agent of the biguanide class, metformin, acts by decreasing hepatic glucose production, decreasing intestinal glucose absorption, and improving insulin sensitivity. It offers low risk of hypoglycemia, and doses between 2,000 to 2,500 mg/day have shown good antihyper-

glycemic efficacy. Due to risk of acidosis, U.S. prescribing information states that metformin is contraindicated in men and women with serum creatinine ≥1.5 mg/dL and ≥1.4 mg/dL, respectively, or if the creatinine clearance is "abnormal." FDA, however, does not define a specific cutoff for creatinine clearance. AACE/ACE proposes discontinuation of metformin in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. Furthermore, AACE/ACE recommends against metformin use in patients with stage 3B, 4, or 5 chronic kidney disease (CKD). A small percentage of metformin users may experience dysfunction in vitamin B12 absorption, which often leads to anemia and/or development of peripheral neuropathy. Vitamin B12 levels should be monitored in all patients taking metformin; patients affected by malabsorption should receive vitamin B12 supplementation. Metformin should be at the base of any T2D regimen, whether used as monotherapy or in combination, unless contraindicated.

GLP-1 Agonists. AACE/ACE recommends GLP-1 receptor agonists, or incretin mimetics, as appropriate treatment options for T2D. Agents in this class include albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Byetta), and liraglutide (Saxenda, Victoza). GLP-1 receptor agonists exert their effect by mimicking the action of incretin hormone, which increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, increases beta-cell growth and replication, delays gastric emptying, and increases satiety. GLP-1 receptor agonists offer strong A1C-lowering properties, are available in various formulations, and are often associated with weight loss and blood pressure reduction. In addition to a low risk of hypoglycemia, GLP-1 receptor agonists also decrease fluctuations in both preprandial and postprandial glucose levels. Although no studies have confirmed that incretin agents cause pancreatitis, AACE/ACE recommends GLP-1 receptor agonists be used cautiously, if at all, in patients with a history of pancreatitis and should be discontinued upon development of acute pancreatitis. Because of their ability to delay gastric emptying, patients with gastroparesis or severe gastroesophageal reflux disease (GERD) require close monitoring and dosage adjustments. Incretin mimetics may be used as monotherapy in patients with contraindications to metformin. They may also be used in conjunction with metformin as dual therapy in cases where glycemic targets are not met after three months.

SGLT-2 Inhibitors. Sodium glucose cotransporter-2 (SGLT-2) inhibitors are another option in treatment of T2D. Agents such as canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance) remove glucose by inhibiting the cotransporter responsible for filtered glucose resorption and decreasing the renal glucose threshold. Excess glucose is then excreted in the urine. SGLT-2 inhibitors have been observed to decrease A1C, weight, and systolic blood pressure. Agents in this class carry an FDA black box warning regarding increased risk of diabetic ketoacidosis (DKA) and serious urinary tract infection (UTI). DKA has been reported in both type 1 and type 2 diabetic patients with slight hyperglycemia; investigations into post-marketing reports are ongoing. Despite the FDA black box warning, AACE/ACE supports SGLT-2 inhibitors as third-line therapy for T2D after an expert consensus group found the incidence of DKA to be infrequent. SGLT-2 inhibitors may be used as monotherapy in patients in need of an alternative agent for metformin or GLP-1 receptor agonists. They may also be used in combination therapy.

DPP-4 Inhibitors. Dipeptidyl peptidase 4 (DPP-4) inhibitors are the next therapeutic option for T2D treatment. Agents in this class include alogliptin (Nesina), linagliptin (Tradjenta), saxagliptin (Onglyza), and sitagliptin (Januvia). DPP-4 inhibitors enhance circulating incretin levels, thereby stimulating glucose-dependent insulin synthesis and suppressing glucagon secretion. DPP-4 inhibitors offer a modest reduction in A1C with low risk of hypoglycemia and are considered weight-neutral. All agents except linagliptin are renally eliminated; therefore, patients with renal dysfunction will require dosage adjustments. DPP-4 inhibitors should be used with caution in patients with a history of pancreatitis. DPP-4 inhibitors may be initiated as monotherapy in cases of contraindication or intolerance to metformin, GLP-1 analogs or SGLT-2 inhibitors.

In April 2016, FDA released a safety communication warning that T2D medications containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. The FDA warning is based on two large clinical trials conducted in patients with heart disease. Each trial showed that more patients who received saxagliptin- or alogliptin-containing medications were hospitalized for heart failure compared to patients who received placebo.

In light of the new warning, patients taking these medications should contact a healthcare professional right away if they develop signs or symptoms of heart failure, such as unusual shortness of breath, tiredness, fatigue, or unexplained weight gain. Patients should not stop taking their medications without first talking to a healthcare professional, but providers may consider stopping these agents in patients who develop heart failure.

This is not the first issue addressed in the *Warnings and Precautions* labeling of the DPP-4 inhibitors. Most recently in August 2015, FDA warned that this class of antihyperglycemic agents may cause severe and disabling joint pain. In a search of the FDA Adverse Event Reporting System (FAERS) database, researchers

Table 2
Selected insulin products

Type of Insulin	Brand Name	Generic Name	Onset†	Peak Action†	Duration of Action†
Rapid-Acting	Apidra	glulisine	20-30 mins	60-90 mins	3-5 hrs
	HumaLOG	lispro	5-20 mins	60-180 mins	3-5 hrs
	NovoLOG	aspart	10 mins	60-180 mins	3-5 hrs
Short-Acting	Humulin R	regular	30-60 mins	2-5 hrs	4-12 hrs
	Novolin R	regular	30-60 mins	2-5 hrs	4-12 hrs
Intermediate-Acting	Humulin N	NPH	1-5 hrs	4-12 hrs	14-24 hrs
	Novolin N	NPH	1-5 hrs	4-12 hrs	14-24 hrs
Long-Acting	Basaglar‡	glargine	2-4 hrs	no peak	22-24 hrs
	Lantus	glargine	2-4 hrs	no peak	22-24 hrs
	Levemir	detemir	2-4 hrs	2-9 hrs	up to 24 hrs
Ultra-Long-Acting	Tresiba‡	degludec	30-90 mins	no peak	up to 40 hrs
Mixtures	Humulin 70/30	NPH + reg	30-60 mins	2-12 hrs	18-24 hrs
	Novolin 70/30	NPH + reg	30-60 mins	2-12 hrs	18-24 hrs
	Humalog Mix 50/50	50% lispro protamine + 50% lispro	15-30 mins	0.8-4.8 hrs	14-24 hrs
	Humalog Mix 75/25	75% lispro protamine + 25% lispro	10-30 mins	1-6.5 hrs	14-24 hrs
	Novolog Mix 70/30	70% aspart protamine + 30% aspart	10-20 mins	1-4 hrs	18-24 hrs
	Ryzodeg 70/30‡	70% degludec + 30% aspart	14 mins	72 mins	≥ 24 hrs

†Onset, peak, and duration of action may vary between products for each patient.
‡Newly-approved insulin product

noted several cases of severe joint pain associated with the use of DPP-4 inhibitors. Patients developed symptoms from one day to years after initiating the drugs. After the agents were discontinued, their symptoms were relieved, usually in less than a month.

Again, patients should not stop taking DPP-4 inhibitors without first talking to their healthcare professionals, but are advised to contact a provider right away if they experience severe and persistent joint pain. These agents should be considered as possible causes of joint pain and discontinued if appropriate. Healthcare professionals and patients are urged to report side effects involving these medications to the FDA MedWatch program.

Thiazolidinediones. Thiazolidinediones (TZDs) are the fifth option and the only antihyperglycemic agents that directly reduce insulin resistance. Agents such as pioglitazone (Actos) and rosiglitazone (Avandia) offer relatively potent A1C-lowering effects, carry a low risk of hypoglycemia, and confer robust glycemic effects. Pioglitazone may confer additional benefits in cardiovascular disease. Although TZDs may be considered as monotherapy in certain patient populations, their general use is limited due to dose-related adverse effects associated with the class, including weight gain, increased risk of bone fracture in postmenopausal women and elderly men, and increased risk of chronic edema or heart failure. Adverse effects may be managed by prescribing moderate doses.

Other Agents. Alpha-glucosidase inhibitors (AGIs) and sulfonylureas (SFUs) have largely fallen out of favor due to unfavorable adverse effects. AGIs, such as acarbose (Precose) and miglitol (Glyset), offer modest A1C reduction and have low risk of hypoglycemia; however, adverse effects such as bloating, flatulence, and diarrhea have limited their use in the United States. Conversely, SFUs, such as glipizide (Glucotrol), glimepiride (Amaryl), and glyburide (Glynase),

are relatively potent A1C reducers, but are associated with weight gain and carry the highest risk of serious hypoglycemia. Colesevelam (Welchol), a bile acid sequestrant, modestly lowers glucose and does not cause hypoglycemia; however, its use is limited due to a high incidence (>10 percent) of gastrointestinal intolerance and its ability to exacerbate serum triglyceride (TG) levels in patients with pre-existing TG elevations. Bromocriptine (Cycloset, Parlodel) has minor glucose-lowering properties and low risk of hypoglycemia but may cause nausea and orthostasis, limiting its use.

Insulin. Patients with long-standing T2D or patients who take more than two antihyperglycemic agents are unlikely to meet and maintain their A1C goals without eventually requiring insulin. In these cases, a once daily dose of basal insulin should be added. Insulin is the most potent glucose-lowering agent. Initiating insulin therapy must be patient-specific, taking into consideration the patient's motivation, comorbidities, age, general health, and cost effectiveness. Insulin regimens should be reassessed frequently to reach the target glucose level while avoiding hypoglycemia. Adjustments in insulin regimens should be made based on individual patient response.

Common dual insulin regimens include concomitant administration of rapid-acting insulin plus basal insulin. Patients whose insulin regimens fail to provide adequate coverage may need combination therapy with an additional antihyperglycemic agent. In combination with insulin therapy, both GLP-1 receptor agonists and SGLT-2 inhibitors further propagate glucose reduction without the risk of hypoglycemia. Incretin mimetics also increase endogenous insulin secretion in response to meals, lowering postprandial hyperglycemia. Within the last year, several new antihyperglycemic agents have been approved by FDA. Table 2 lists available insulin products along with their onset, peak, and duration of action.

New Antihyperglycemic Agents

Basaglar *(insulin glargine).* A new insulin glargine 100 units/mL (U-100) injection, Basaglar, was approved in December 2015 to improve glycemic control in adults and pediatric patients with T1D and adults with T2D. Basaglar contains the same amino acid sequence as Lantus, a previously-approved insulin glargine U-100 product, and is considered a follow-on biologic product in the United States. Basaglar has been available in the U.S. since December 2016.

Basaglar is the first insulin product approved through an abbreviated approval pathway under the Federal Food, Drug, and Cosmetic Act. In its application for approval, it was demonstrated that Basaglar was sufficiently similar to previously approved insulin glargine products. Data included two clinical trials enrolling 535 and 759 patients with T1D and T2D, respectively, in which Basaglar was compared to previously approved insulin glargine U-100 products. At trial completion for both studies, Basaglar provided a mean reduction in A1C that was non-inferior to that achieved with the comparator insulin glargine U-100 products. Basaglar is provided as a prefilled 3 mL delivery device and is to be administered as a subcutaneous injection once daily at the same time each day. The recommended starting dose of Basaglar in patients with T1D should be approximately one-third of the total daily insulin requirements, and rapid-acting insulin should be used to make up the remainder of the daily requirements. For patients with T2D, the recommended starting dose is 0.2 units/kg or up to 10 units once daily. Dosing and timing of other insulins and other antihyperglycemic agents may need to be adjusted when starting Basaglar. If changing patients from another insulin glargine U-100 product, the dose of Basaglar should be the same as the previous product.

Tresiba *(insulin degludec).* The first ultra-long-acting insulin analog, insulin degludec (Tresiba), was approved in September 2015. Similar to previously-approved basal insulins, insulin degludec is indicated to improve glycemic control in adults with T1D or T2D. Insulin degludec is available in both 100 units/mL (U-100) and 200 units/mL (U-200) prefilled pen devices, and is to be administered as a once daily subcutaneous injection at the same time each day. Starting doses for patients with T1D or T2D are the same as other long-acting insulin products and dosing should be individualized based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control. No conversion is needed when using the insulin degludec U-100 or U-200 pens, as their dose windows show the number of insulin units to be administered.

To evaluate its efficacy in patients with T1D, insulin degludec was evaluated in three randomized, controlled trials, in which the long-acting insulin was given once daily in combination with rapid-acting insulin at mealtimes. Two of the studies compared the drug to insulin glargine, and the third compared it to insulin detemir. To evaluate its efficacy in T2D, six clinical trials were conducted to compare insulin degludec to previously-approved long-acting insulins as an add-on to oral antihyperglycemic drug regimens and/or in combination with rapid-acting insulins at mealtime. Results of the studies in both T1D and T2D determined that patients treated with insulin degludec achieved levels of glycemic control similar to those achieved with previously-approved long-acting insulins.

Ryzodeg 70/30 *(insulin degludec/insulin aspart).* A mixture of insulin degludec and insulin aspart, a rapid-acting insulin, was also recently approved by FDA under the brand name Ryzodeg 70/30. It improves glycemic control in patients with T1D and T2D. Dosing

of insulin degludec/insulin aspart should be individualized and titrated based on each patient's specific needs and glycemic control goals. The U-100 product is available as a 3 mL prefilled pen and is to be administered subcutaneously once or twice daily with any main meal; a rapid-acting insulin may be administered at other meals if needed.

The efficacy of insulin degludec/insulin aspart used in combination with mealtime insulin in patients with T1D was evaluated in one 26-week controlled trial, in which 529 patients were randomized to receive insulin degludec/insulin aspart, or insulin detemir once daily. Results of the trial determined that insulin degludec/insulin aspart was non-inferior to insulin detemir in providing glycemic control in patients with T1D. For use in T2D, the efficacy of insulin degludec/insulin aspart administered once or twice daily used in combination with oral antihyperglycemic agents was evaluated in four randomized controlled trials. The studies determined that patients treated with insulin degludec/insulin aspart achieved levels of glycemic control similar to those treated with insulin glargine, insulin detemir and biphasic insulin aspart.

Hypersensitivity reactions including anaphylaxis have been reported with insulin products. Should symptoms of hypersensitivity occur, treatment should be discontinued and the patient should seek immediate medical care. Insulins also have the potential to cause hypokalemia. Therefore, potassium levels should be monitored in patients at risk, including patients using other potassium-lowering medications. The most common adverse reaction associated with the use of all insulins is hypoglycemia. Thus, insulin products are contraindicated in periods of hypoglycemia. Changes in insulin strength, manufacturer, type or method of administration may affect glycemic control. These changes, therefore, should be made cautiously and only under close medical supervision.

Due to limited data available for the use of the new insulin products in pregnant women and because there are potential risks to both mother and fetus in the case of poorly controlled diabetes, these agents should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No dosage adjustments for renal or hepatic impairment are provided in manufacturer labeling; however, more frequent glucose monitoring and dose adjustments may be necessary in these patients.

When counseling patients on proper preparation and use of insulin products, it is important to offer guidance on how to correctly administer the injection, including the importance of aseptic technique. All basal insulins should be administered subcutaneously into the abdominal area, thigh, or deltoid muscle, and patients should be instructed to rotate injection sites daily to reduce the risk of lipodystrophy (abnormal or degenerative conditions of the body's adipose tissue). Patients must also be educated to recognize and manage episodes of hypoglycemia when using any insulin product.

***Adlyxin** (Lixisenatide).* The new GLP-1 receptor agonist, lixisenatide [Adlyxin], was approved in July 2016. Lixisenatide is a once-daily injection indicated to improve glycemic control, along with diet and exercise, in adults with T2D. Like other GLP-1 receptor agonists, lixisenatide increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying. Lixisenatide is initiated at 10 micrograms once daily for 14 days. On day 15, the dose is increased to the maintenance dose of 20 micrograms once daily. It is injected subcutaneously in the abdomen, thigh or upper arm, and is to be administered within one hour before the first meal of each day. Serious hypersensitivity reactions, including anaphylaxis, angioedema and urticaria, have been reported in clinical trials. If symptoms of hypersensitivity occur, treatment should be discontinued and the patient should seek immediate medical care. The most common adverse reactions associated with the use of lixisenatide are nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia. Other reported adverse reactions (2 to 5 percent of lixisenatide-treated patients and more frequently than placebo) include dyspepsia, constipation, abdominal distension, and abdominal pain.

Because lixisenatide delays gastric emptying, it may impact absorption of concomitantly administered oral medications. Consequently, medications that are particularly dependent on threshold concentrations for efficacy, such as antibiotics or medications for which a delay in effect is undesirable, such as acetaminophen, should be administered one hour before lixisenatide. Oral contraceptives should also be taken at least one hour before or 11 hours after the dose of lixisenatide.

Lixisenatide is not indicated for use in patients with T1D or for treatment of diabetic ketoacidosis. Concurrent use with short-acting insulin has not been studied. Additionally, lixisenatide has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis or in patients with gastroparesis, and thus is not recommended in these patients.

Due to limited data available for the use of lixisenatide in pregnant women, the drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No dosage adjustment is required for patients with mild, moderate, or severe renal impairment; however, these patients should be closely monitored for adverse reactions and changes in renal function as these patients tend to have a higher incidence of hypoglycemia, nausea and vomiting. No data are available for patients with acute or chronic hepatic impairment. Lixisenatide is primarily eliminated through glomerular filtration and proteolytic degradation with a terminal half-

life of approximately three hours.

Lixisenatide has been studied as monotherapy, in combination with oral antihyperglycemic medications, and in combination with basal insulin. Monotherapy was evaluated in a 12-week double-blind trial, in which 241 patients with T2D, inadequately controlled on diet and exercise, were randomized to receive lixisenatide 20 mcg once daily or placebo. Treatment resulted in a statistically significant reduction of 0.83 percent in A1C from baseline to week 12, compared to a 0.18 percent reduction with placebo.

To evaluate its use in combination with oral antihyperglycemic medications, lixisenatide was investigated in four placebo-controlled studies as an add-on to different therapies, including metformin with or without a sulfonylurea, a sulfonylurea with or without metformin, and pioglitazone with or without metformin. In each of these studies, lixisenatide demonstrated statistically significant reductions in A1C compared to placebo from baseline to trial completion. In another study, metformin plus lixisenatide was compared to metformin plus exenatide, a previously approved GLP-1 receptor agonist. In this case, lixisenatide produced lower A1C reductions than exenatide 10 mg twice daily.

Lixisenatide was also compared to basal insulin with and without oral antihyperglycemic agents. Compared to placebo, lixisenatide demonstrated statistically significant reductions in A1C when added to basal insulin regimens; however, when the drug was compared to insulin glulisine three times daily added to basal insulin, it provided significantly less A1C reduction from baseline.

When counseling patients on proper preparation and use of lixisenatide, it is important to offer guidance on how to correctly administer the injection, including the importance of aseptic technique. It is supplied in a green starter pen (50 mcg/mL) that delivers 14 doses of 10 mcg, and a burgundy maintenance pen (100 mcg/mL) that delivers 14 doses of 20 mcg each. Prior to the first use, lixisenatide should be stored in the refrigerator and kept in the original package to protect it from light. Each new pen must be activated prior to use. After activation, it can be stored at room temperature and should be discarded 14 days after first use.

Synjardy *(empagliflozin/metformin).* FDA has approved a new combination medication containing metformin for the treatment of adults with T2D. Synjardy, approved in August 2015, combines metformin with empagliflozin, an SGLT-2 inhibitor. It is indicated as adjunct to diet and exercise to improve glycemic control when treatment with both drugs is appropriate. There have been no efficacy studies conducted; however, the bioequivalence of the combination product to empagliflozin and metformin coadministered as individual tablets was demonstrated in healthy subjects.

Empagliflozin/metformin is supplied as a tablet for oral administration. Dosing is based on the patient's current antihyperglycemic regimen. Because the drug contains both empagliflozin and metformin, it may cause adverse reactions such as urinary tract infections, diarrhea, nausea, vomiting, abdominal discomfort, and indigestion. It also comes with a boxed warning for the risk of lactic acidosis due to metformin accumulation. This risk is increased with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.

The new combination adds to a list of antihyperglycemic agents that are already combined with metformin, including other SGLT2 inhibitors, SFUs, DPP-4 inhibitors, TZDs, and repaglinide. Unless contraindicated, metformin remains the first-line oral agent recommended in T2D. If target A1C is not met after approximately three months, adding a second oral agent or insulin should be considered, and a third agent may be added if glycemic control continues to be unachievable. There are patients with diabetes who require more than one agent to control their blood glucose levels. Having several metformin combinations available, including the newest combination may help decrease a patient's pill burden and improve compliance.

Summary

The incidence of diabetes in the United States has grown rapidly and steadily. Patients with poor glycemic control are at significantly higher risk of developing complications such as neuropathy, blindness, and renal failure. Therapy should include a combination of lifestyle modifications and medication. Several antihyperglycemic agents are available; however, pharmacologic therapy should be individualized to meet the patient's needs. Pharmacists have a unique opportunity to aid in the management of diabetes and the associated complications. For further details, of the AACE/ACE diabetes guidelines, visit: https://www.aace.com/sites/all/files/diabetes-algorithm-executive-summary.pdf.

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continuing education quiz

2016 AACE/ACE Guidelines on Type 2 Diabetes Management and New Glycemic Control Agents

1. Which of the following types of diabetes is characterized by the body's ineffective use of endogenous insulin?
   a. Type 1 diabetes b. Type 2 diabetes

2. Sleep deprivation has no effect on insulin resistance.
   a. True b. False

3. For most patients, AACE/ACE supports an A1C goal of:
   a. ≤6.5 percent. c. ≥7.0 percent.
   b. >6.5 percent. d. ≥8.0 percent.

4. Which of the following agents is considered first-line therapy in treating type 2 diabetes?
   a. Basal insulin c. GLP-1 agonists
   b. Empaglifozin d. Metformin

5. Which of the following agents carries an FDA black box warning regarding increased risk of diabetic ketoacidosis?
   a. SGLT-2 inhibitors c. GLP-1 agonists
   b. DPP-4 inhibitors d. Thiazolidinediones

6. FDA issued a safety warning that T2D medications containing saxagliptin and alogliptin may increase the risk of:
   a. serious hypoglycemia. c. heart failure.
   b. hypokalemia. d. urinary tract infections.

7. Which of the following directly reduces insulin resistance?
   a. Acarbose c. Metformin
   b. Glipizide d. Rosiglitazone

8. All of the following adverse effects of alpha-glucosidase inhibitors have limited their use in the U.S. EXCEPT:
   a. diarrhea. c. flatulence.
   b. nausea. d. bloating.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b]	6. [a] [b] [c] [d]	11. [a] [b] [c] [d]
2. [a] [b]	7. [a] [b] [c] [d]	12. [a] [b] [c] [d]
3. [a] [b] [c] [d]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b] [c] [d]	9. [a] [b] [c] [d]	14. [a] [b] [c] [d]
5. [a] [b] [c] [d]	10. [a] [b] [c] [d]	15. [a] [b] [c] [d]

❑ **I am enclosing $5 for this month's quiz made payable to: Ohio Pharmacists Association.**

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no If no, why?_____
4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
5. How long did it take you to read this lesson and complete the quiz? _____
6. Comments/future topics welcome.

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9. All of the following are true for insulin glargine EXCEPT:
   a. it should be administered once weekly.
   b. the recommended starting dose in patients with T1D should be approximately 1/3 of the total daily insulin requirements, with rapid-acting insulin making up the remainder of the daily requirement.
   c. it improves glycemic control in pediatric patients with T1D.
   d. the dosing and timing of other insulins may need to be adjusted when starting this agent.

10. Tresiba has a duration of action of up to:
   a. 4 hours. c. 24 hours.
   b. 18 hours. d. 40 hours.

11. Due to an increased risk of hypokalemia, potassium levels should be monitored in patients receiving agents from which of the following classes of drugs?
   a. Insulin c. DPP-4 inhibitors
   b. TZDs d. GLP-1 agonists

12. All of the following are appropriate to convey when counseling patients on the use of insulin products EXCEPT:
   a. the importance of aseptic technique.
   b. to rotate injection sites to reduce the risk of lipodystrophy.
   c. all basal insulins should be administered intramuscularly in the thigh or deltoid muscle.
   d. how to recognize and manage episodes of hypoglycemia.

13. Lixisenatide should be administered:
   a. daily with the largest meal.
   b. once or twice daily with any main meal.
   c. at the same time every day.
   d. within one hour before the first meal of the day.

14. The most common adverse reactions associated with lixisenatide include all of the following EXCEPT:
   a. headache. c. dizziness.
   b. bloating. d. diarrhea.

15. Synjardy comes with a boxed warning for the risk of:
   a. liver impairment. c. heart failure.
   b. lactic acidosis. d. urinary tract infections.

To receive CPE credit, your quiz must be received no later than February 15, 2020. A passing grade of 80% must be attained. CPE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CPE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.