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STATEMENT OF FINANCIAL DISCLOSURE

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Pharmacologic Management of Type 2 Diabetes Mellitus: Part 1

This is two-part series of articles will address pharmacological agents, except insulin, used to manage type 2 diabetes mellitus. Part 1 covers sodium glucose co-transporter-2 inhibitors, incretin-based therapies, amylin analog, and dopamine receptor agonists. Part 2 focuses on biguanides, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and bile acid resins, as well as the authors' treatment recommendations.

Diabetes has reached epidemic levels in the United States and worldwide, and an estimated 9.3% of the world population has diabetes.[1] During the last 20 years, diabetes rates increased 45%, with the greatest increases in adults older than 65 years of age. More than one-fourth of seniors have diabetes.[2] By 2050, an estimated one in three Americans are projected to have diabetes.[1]

What is contributing to this increase? Diabetes rates are closely tied to excessive body weight. More than two-thirds of Americans are overweight or obese.[1] In addition, a third of Americans and half of those older than 65 years of age have prediabetes. Unfortunately, approximately 90% of patients with prediabetes are unaware of their diagnosis, thus making effective intervention unlikely.[1] Patients with type 2 diabetes and prediabetes often are diagnosed with routine lab testing. Most individuals with impaired glucose tolerance remain asymptomatic during the earliest stages of the disease.

The beginning of the 21st century has been an exciting time for diabetes medications. Since 2005, 16 new medications and six new classes of medications have been approved for type 2 diabetes.[3] Although diabetes once was considered a disease of only insulin resistance and exhausted beta cells, it is now known that at least eight pathophysiologic mechanisms are at play in type 2 diabetes.[4]

Despite a better understanding of the disease and more available treatment options, only about half of Americans have their diabetes in control (A1c < 7.0%).[5] Diabetes is a complex disease that is largely self-managed and requires a substantial amount of daily work, including monitoring blood glucose, taking medications, eating a healthy diet, and keeping physically active. Some estimates indicate it takes patients more than three hours per day to complete the self-care activities recommended by diabetes educators.[6]

This article will review FDA-approved medications for type 2 diabetes, including key features of each agent, guidelines for use in clinical practice, warnings and contraindications, and recommendations from the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and the European Association for the Study of Diabetes.[7-10] This review will not include discussion of insulin, as it has been extensively reviewed in previous issues.[11,12] Since there are so many new medications and it is getting increasingly difficult to keep up, the authors will discuss the new medications first and

EXECUTIVE SUMMARY

Considering the burgeoning epidemic of diabetes in this country and the increasing development of diabetic pharmacological treatments, it is incumbent upon the primary care physician to be conversant with the choices available.

- Since 2005, 16 new medications and six new classes of drugs have been approved for type 2 diabetes.
- Despite better understanding of the disease and an increased armamentarium of treatment options, only about half of Americans have their diabetes in control (A1c < 7.0%).
- The common classes of antihyperglycemic medication other than insulin include insulin sensitizers, insulin secretogogues, incretin agents, agents impacting the GI tract, renal glucose reabsorption inhibitors and others.

work back to the older medications. This review will explore why the new medications are important but also share why we should not give up on some of the older medications.

Pharmacologic Treatment for Diabetes

What Do I Need to Know About the New Classes of Diabetes Medications?

Newer diabetes agents are not necessarily more efficacious than older agents, but they do have distinctive benefits, mostly related to the non-glycemic properties and fewer patient-centered side effects. For example, many of the newer agents have lower rates of hypoglycemia compared to sulfonylureas, which is important because hypoglycemia is a major risk for morbidity and mortality in type 2 diabetics. In addition, some newer agents are associated with weight loss, which was uncommon with older diabetes agents. Others can help reduce blood pressure, which is often hard to control in type 2 diabetes. Finally, many newer agents have less frequent dosing, ranging from once a day to once a week, a feature that may improve adherence to therapy.

Diabetes medications used to be divided into insulin sensitizers and insulin secretagogues. Table 1 shows one classification of the agents for type 2 diabetes. Newer agents now can address the many parallel pathophysiologic processes to type 2 diabetes.[4]

Since most of the newer diabetes medications are patent-protected and name-brand, they are more expensive than older generic medications. Many medications used for managing hyperglycemia, such as sulfonylureas and metformin, have been around in some shape or form since the 1950s to the 1970s. However, the newer agents appear to work faster and cause less weight gain and lower risk of hypoglycemia. The AACE guidelines suggest that safety and efficacy should prevail in decision-making. Yet, for many individuals, the cost of newer medications may limit their use. Furthermore, some insurance plans require a stepwise approach to treatment for prescription coverage. Table 2 provides a general estimation of the costs of each of the type 2 diabetes medications. Tier 1 drugs with the lowest patient copays are sulfonylureas and metformin. The economics can be quite complex: Many companies have programs for indigent patients, distribute coupons, and provide free samples, whereas some HMOs can be quite stringent and may require pre-authorization or letters of appeal for the more expensive diabetic agents from their formularies.

Sodium Glucose Co-Transporter-2 Inhibitors

Sodium glucose co-transporter-2 (SGLT2) inhibitors are the newest class of medications available for managing type 2 diabetes. These oral agents target the kidneys to lower blood glucose levels through an insulin-independent mechanism.

Plasma glucose usually is maintained in a relatively narrow range between 70-160 mg/dL (3.9-8.9 mmol/L). This involves a delicate balance between glucose production (liver and kidney), intestinal absorption, renal reabsorption, and glucose utilization in body tissues. In a normal healthy adult, the kidneys can filter approximately 200 grams of glucose/day (mean glucose 100 mg/dL x 180 L/day).[14] In euglycemic patients, essentially all filtered glucose is reabsorbed at the proximal tubule.[14] Most of the glucose is reabsorbed in the proximal convoluted tubule by SGLT2 (90%), and the rest is absorbed in the distal aspect of the proximal convoluted tubule by SGLT1 (10%). The normal filtered glucose load in a person without diabetes is approximately 125 mg/min, but this can rise when the ambient glucose increases or if the glomerular filtration rate (GFR) increases. If the plasma glucose exceeds 180-200 mg/dL, the reabsorptive threshold is exceeded and excess glucose is excreted into the urine.[14] In type 2 diabetes, an abnormal compensatory mechanism occurs. The renal threshold for glucose reabsorption rises to 240 mg/dL.[15] Since SGLT2 is overexpressed in the proximal tubule, the reabsorption capacity of glucose is increased, resulting in a rise in plasma glucose for patients who are already insulin resistant.[16,17]

This class of medications works independent of pancreatic function (insulin secretion) or liver function (glucose production), making it complementary to other classes of medications. Since it is not dependent on functional beta cells, it can be used for people with long-standing diabetes for whom other medications working on insulin secretion fail. Further, because it is independent of insulin, it has a low risk of hypoglycemia. With glucosuria as the net effect of this class of medications, many people lose weight as a response to taking SGLT2 inhibitors. The novel mechanism allows truly synergistic effects. In addition to lowering fasting glucose, postprandial glucose, and A1c, SGLT2 inhibitors can lead to weight loss, reduced blood pressure, and reduction in serum uric acid levels (uric acid is a marker to indicate insulin resistance).[53] The three medications in this class currently approved in the United

Table 1. Classes of Anti-hyperglycemic Medications

Functional Class	Insulin Sensitizer	Insulin Secretagogues	Incretin Agents	Agents Affecting GI Tract	Renal Glucose Reabsorption Inhibitors	Other
Description of the Class	Makes the body use insulin more effectively, which lowers both glucose and insulin	Increase in insulin secretion independent of glucose level	Insulin secretion based on glucose level, suppression of glucagon and reducing hepatic glucose production	Change in absorption of glucose from the GI tract	Inhibits glucose reabsorption in the kidney	CNS effect creating satiety
Agents	Biguanide	Sulfonylureas	DPP-4 inhibitors	Alpha glucosidase inhibitors	SGLT2 inhibitors	Dopamine agonist
	Thiazolidinediones	Meglitinides	GLP-1 receptor agonists	Bile acid resins		
			Amylin analogs			

States are canagliflozin, dapagliflozin, and empagliflozin. They are all once-daily oral medications.

Therapeutic/Clinical Indications

SGLT2 inhibitors can be used as second-line treatment after metformin and therapeutic lifestyle changes. If the patient has contraindications or intolerance to metformin, SGLT2 inhibitors can be given as a monotherapy, per the AACE and ADA guidelines.[18,19] In many practices, these agents typically are given as a second- or third-line medication after metformin, sulfonylureas, and oral dipeptidyl peptidase-4 (DPP4) inhibitors.

The ADA guidelines suggest that SGLT2s can be used as second-line therapy in patients with type 2 diabetes. AACE suggests the use of SGLT2s in patients with A1c > 7.5 %. The drugs can be given as monotherapy, dual therapy, or triple therapy. In patients with more advanced disease, SGLT2s should be considered before using DPP4s, which are less effective in later stage diabetes.

Patients with normal kidney function (eGFR > 90 mL/min), a need for increased glucose control, and high blood pressure may benefit from this class of medication. Since SGLT2 inhibitors are associated with volume depletion and orthostatic hypotension, individuals at high risk for falls or injury due to falls should avoid this class of medications.[16] In addition to the anti-hyperglycemic effects, overweight or obese patients with type 2 diabetes may benefit from this class of medication through weight loss. Weight loss occurs because SGLT2s increase urinary glucose excretion by 100 grams per day, which is the equivalent of losing 400 calories per day in the urine.

Although there is potential concern about worsening diabetic nephropathy due to permissive glucosuria, this has not been seen in short-term trials with this class of oral hypoglycemic agents. Diabetic nephropathy is a glomerular disease. Because of increased excretion of glucose, the net GFR is reduced with these agents. The resulting glucosuria in the tubules does not worsen nephropathy. In fact, studies have shown that SGLT2 inhibitors improve diabetic nephropathy.[20]

Table 2. Costs of Select Classes of Medications for Type 2 Diabetes[13]

Class of Agents	Cost*
Sodium Glucose Co-Transporter 2 Inhibitors	$$
Glucagon-Like Peptide 1 Receptor Agonists	$$$
Dipeptidyl Peptidase-4 Inhibitors	$$
Amylin Analog	$$$
Dopamine Receptor Agonist	$$
Biguanide	$
Thiazolidinediones	$$
Sulfonylureas	$
Meglitinides	$$
Alpha-Glucosidase Inhibitors	$$
Bile Acid Sequestrants	$$$

*$ least costly to $$$ most costly

Key Studies/Trials

A systematic review and meta-analysis of clinical trials comparing SGLT2 inhibitors with placebo (45 studies, n = 11,232) reported improved glycemic control, reduced body mass, and lower blood pressure when using SGLT2 inhibitors.[27]

Recent data published in summer 2016 demonstrated both empagliflozin

and canagliflozin reduced progression of chronic kidney disease and microalbuminuria.[28,54] In the landmark Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) outcome study, empagliflozin lowered rates of nephropathy progression and reduced risk of major adverse cardiovascular events compared to placebo when added to standard type 2 diabetes care.[28] Those randomized to empagliflozin (compared to placebo) had a 14% reduction in risk of composite cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. This was largely because of a 38% reduction in cardiovascular death.[21] These are important results, as this was the first trial to show significant macrovascular cardiovascular benefit from a new class of anti-hyperglycemic agents.

Safety Concerns

SGLT2 agents are filtered through the glomerulus, so they require a functioning kidney to reach their site of action. Patients with renal impairment of eGFR < 45 mL/min/1.73 m^2 or patients on dialysis should not take this class of medications.

Currently, these medications are indicated only in type 2 diabetes. There have been reports of patients developing "euglycemic" diabetic ketoacidosis on these agents. These reports have occurred largely in type 1 diabetics (off-label), but also have been reported in type 2 diabetics, mostly when the insulin dosage has been reduced or stopped. Researchers believe that since SGLT2 agents work independent of insulin, they can lower glucose enough so that the exogenous insulin dose also is reduced while there is a compensatory increase in glucagon, which may make the person relatively insulinopenic for cellular functions, leading to acidosis.

Despite significant controversy regarding the plausibility of the mechanism, in 2015 the FDA strengthened its warning for canagliflozin related to increase in bone fractures.[22] The 2016 ADA guidelines suggest considering a patient's risk of fracture prior to initiation.[18] The associated risk of bone density loss with canagliflozin was seen as early as 12 weeks after treatment initiation. It is hypothesized that a bone density loss may be caused by a decrease in serum parathyroid hormone and 1,25-dihydroxyvitamin D levels.[23] Further study is needed to explore this relationship. Other medications in this class are being evaluated for bone density loss.

Renal/Hepatic Dose Recommendations

None of the medications in this class should be used if the eGFR is < 45 mL/min/1.73m^2. Patients with reduced renal function with eGFR 45-60 mL/min should limit the daily dose of canagliflozin to 100 mg. Patients on empagliflozin may take 10 mg and 25 mg doses with eGFR > 45mL/min/1.73m^2. Dapagliflozin should be discontinued when eGFR is below 60 mL/min/1.73m^2. Renal function should be monitored and SGLT2 inhibitors should be discontinued if eGFR remains persistently below 45 mL/min/1.73 m^2.

The SGLT2 inhibitors canagliflozin and dapagliflozin carry a boxed warning associated with acute kidney disease. Practitioners should monitor patients closely or use caution when prescribing these agents to patients with decreased blood volume, chronic kidney disease, congestive heart failure, and taking certain medications (diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs).

Common Side Effects

The most common side effects include genital mycotic infections (e.g., vulvovaginal candidiasis and balanitis), urinary tract infections, dehydration, hypotension, and orthostasis.[24-26]

Special Populations

Geriatrics: Patients older than 65 years are at increased risk for symptoms related to intravascular volume depletion, especially at higher doses.[24-26]

Pregnancy and breastfeeding: As a category C medication in pregnancy, SGLT2 inhibitors are best avoided in women who are pregnant or trying to become pregnant. It is unknown if this class of medication is excreted into breast milk. Manufacturer labels recommend that nursing mothers discontinue the drug or discontinue nursing.

The cost of SGLT2 inhibitors is approximately $400 for 30 tablets.[13]

Table 3 describes key characteristics of commercially available SGLT2 inhibitors.

Practical Considerations

Many providers and patients prefer SGLT2 inhibitors because they are once-daily oral medications that lower blood glucose with low rates of hypoglycemia, and they are associated with weight loss. Before starting a patient on an SGLT2 inhibitor, consider confirming that renal function is adequate for the medication to reach the tubules and that the patient does not have a history of recurrent urinary tract infections, vaginal or penile yeast infections, or diabetic ketoacidosis. The most common side effects are likely to occur in the first month, so the patient should be monitored for efficacy and tolerance to the medication. The risk of developing hypoglycemia while on an SGLT2 inhibitor is low unless it is being used with sulfonylureas and/or insulin. The weight loss seen with these agents is greatest initially and will level off as compensatory mechanisms kick in, including increased hepatic glucose production. The drawbacks of this class are cost, lack of efficacy in patients with stage 3B chronic kidney disease, reduced efficacy in elderly patients, and the lack of long-term data.

Incretin-based Therapies

Another important addition to diabetes treatment options is incretin-based therapies, which include DPP-4 inhibitors and injectable glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Incretin-based therapies work via the physiological "incretin" effect, which occurs when polypeptides are released from the gut (GLP-1 and GIP) when a person ingests a meal. The oral load of glucose is more potent in stimulating the release of insulin than an equimolar intravenous administration of glucose, which led to the discovery of incretin (INtestinal seCRETion of INsulin) hormones.[29,30] Endogenous GLP-1 is produced by enteroendocrine L cells of distal

Table 3. Key Characteristics of Commercially Available SGLT2 Inhibitors

	Canaglifozin[25]	Empagliflozin[26]	Dapaglifozin[27]
Boxed Warning	None	None	Acute kidney injury
Contraindications	Severe renal impairment (GFR < 30 mL/minute/1.73 m^2) or dialysis		
Common Side Effects (> 5% of patients)	100 mg dose • Female genital mycotic infections • Urinary tract infections • Increased urination 300 mg • Female genital mycotic infections	• Female genital mycotic infections • Urinary tract infections	5 mg dose • Female genital mycotic infections • Nasopharyngitis • Urinary tract infection 10 mg dose • Female genital mycotic infections • Nasopharyngitis
Warnings and Precautions	Hypotension Ketoacidosis Renal function impairment Hyperkalemia Urosepsis and pyelonephritis Hypoglycemia with insulin and insulin secretagogues Genital mycotic infections Hypersensitivity reaction Bone fracture Increases in LDL	Hypotension Ketoacidosis Renal function impairment Urosepsis and pyelonephritis Hypoglycemia with insulin and insulin secretagogues Genital mycotic infections Hypersensitivity reaction Increases in LDL	Hypotension Ketoacidosis Renal function impairment Urosepsis and pyelonephritis Hypoglycemia with insulin and insulin secretagogues Genital mycotic infections Bone fracture Increases in LDL Bladder cancer
Strengths	100 mg, 300 mg	10 mg, 25 mg	5 mg, 10 mg
Mean A1c Reduction (%)*	100 mg: -0.77 300 mg: -1.03	10 mg: -0.7 25 mg: -0.8	5 mg: -0.8 10 mg: -0.9
Mean Weight Reduction (kg)*	100 mg: -2.8 300 mg: -3.9	10 mg: -2.8 25 mg: -3.2	Data for monotherapy unavailable. In Farxiga plus placebo study: 5 mg: -1.2 10 mg: -1.5
Mean Fasting Serum Glucose Reduction (mg/dL)*	100 mg: -27 300 mg: -35	10 mg: -10 25 mg: -25	5 mg: -24.1 10 mg: -28.8
Dosing	May taper up to 300 mg if GFR > 60 mL/min/1.73 m^2	If 10 mg tolerated, may increase to 25 mg	If 5 mg tolerated, may taper up to 10 mg
Renal Impairment Adjustments	Discontinue if GFR < 45 Max dose GFR 60-45 is 100 mg	Discontinue if GFR < 45 May take up to 25 mg with GFR to 45.	Discontinue if GFR < 60
Hepatic Impairment Adjustments	None		
Pregnancy Considerations	Pregnancy category C, lactation unknown		

ileum and colon, which then rapidly degrades within minutes by DPP-4.[30,32] Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) serum concentrations climb minutes after meals, suggesting a combination of neural and endocrine signals leading to their secretion for maintaining glucose homeostasis.[30,31]

These polypeptides address a number of the pathophysiologic processes in type 2 diabetes, and include stimulating insulin secretion, suppressing glucagon production, slowing down gastric emptying (potentially inducing symptoms of gastroparesis), and signaling satiety in the body. This system is potent and is a main regulatory function in controlling postprandial glucose. The two groups of medications that primarily address the "incretin" effect are 1) DPP-4 inhibitors, which are once-daily oral tablets; and 2) GLP-1 RAs, which are injectable therapies with doses ranging from twice daily to once weekly.

Pharmacologically, DPP-4 inhibitors block the breakdown of the incretin polypeptides, allowing an increase in GLP-1 and GIP to a "high physiologic level." This results in a mild reduction in fasting and a more significant improvement in postprandial glucose (A1c reduction about 0.7%). However, the GLP-1 RAs provide a higher therapeutic level of GLP-1 action, leading to greater reductions in A1c and other additional non-pharmacologic effects, including weight loss and a slight reduction of blood pressure. Despite the additional

Table 4. Key Characteristics of Commercially Available GLP-1 RAs[35-39,56,57]

	Exenatide IR [35]	Exenatide ER[36]	Liraglutide[37]	Dulaglutide[38]	Albiglutide[39]	Lixisenatide[56-57]
Boxed Warning	Risk of thyroid C-cell tumors					Has not been issued by FDA
Contraindications	Patients with a personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) A prior serious hypersensitivity reaction					Hypersensitivity
Common Side Effects (> 5% of patients)	Nausea Hypoglycemia Vomiting Diarrhea Jittery Dizziness Headache Dyspepsia	Nausea Diarrhea Headache Vomiting Constipation Site pruritus Site nodule Dyspepsia	Headache Nausea Diarrhea Anti-liraglutide antibody formation	Nausea Diarrhea Vomiting Abdominal pain Decreased appetite	Upper respiratory tract infection Diarrhea Nausea Site reaction Cough Back pain Arthralgia Sinusitis Influenza	Diarrhea Headache Hypoglycemia when used with insulin or a sulfonylurea
Strengths	5, 10 mcg	2 mg	1.2, 1.8 mg	0.75, 1.5 mg	30, 50 mg	10, 20 mg
Mean A1c Reduction (%)*	Placebo: -0.2 5 mcg: -0.7 10 mcg: -0.9 (At Week 24)	IR 10 mcg: -0.9 ER: -1.6 (At Week 24)	Gli**: -0.5 1.2 mg: -0.8 1.8 mg: -1.1 (At Week 52)	Met****: -0.6 0.75 mg: -0.7 1.5 mg: -0.8 (At Week 26)	Placebo: +0.2 30 mg: -0.7 50 mg: -0.9 (at Week 52)	Placebo: -0.42 20 mg: -0.92 (At Week 24)
Mean Weight Reduction (kg) *	Placebo: -1.5 5 mcg: -2.7 10 mcg: -2.9 (At Week 24)	IR 10 mcg: -1.4 ER: -2.3 (At Week 24)	Gli**: +1.1 1.2 mg: -2.1 1.8 mg: -2.5 (At Week 52)	Met****: -2.2 0.75 mg: -1.4 1.5 mg: -2.3 (At Week 26)	Placebo: -0.7 albiglutide: -0.4 to -0.9 (at Week 52)	Placebo: -1.63 20 mg: -2.63 (At Week 24)
Mean Fasting Serum Glucose Reduction (mg/dL)*	Placebo: -5 5 mcg: -17 10 mcg: -19 (At Week 24)	IR 10 mcg: -5 ER: -25 (At Week 24)	Gli**: -5 1.2 mg: -15 1.8 mg: -26 (At Week 52)	Met****: -24 0.75 mg: -26 1.5 mg: -29 (At Week 26)	Placebo: +18 30 mg: -16 50 mg: -25 (at Week 52)	–
Dosing	Twice daily	Once weekly	Once daily	Once weekly	Once weekly	Once daily
Renal Impairment Adjustments	CrCl*** < 30 mL/min or end-stage renal disease: Do not use		Use with caution; no dose adjustments recommended			Not recommended in patients with severe renal impairment
Hepatic Impairment Adjustments	Renally cleared, hepatic dysfunction does not affect blood concentration					Cleared primarily by kidneys
Pregnancy Considerations	Pregnancy Category C: No adequate and well-controlled studies in pregnant women					No adequate data

* In trials used as monotherapy; changes from baseline
** Gli = glimepiride 8 mg daily
*** CrCl = Creatinine clearance
**** Metformin 1500 – 2000 mg daily
Lixisenatide: Results on mean A1c reduction and mean weight reduction achieved by adding to metformin

benefits, GLP-1 RAs also have more common side effects, including nausea, vomiting, and diarrhea.

Glucagon-Like Peptide-1 Receptor Agonists

Therapeutic/Clinical Indications

The five GLP-1 RAs include exenatide (immediate-release and extended-release), liraglutide, dulaglutide, albiglutide, and lixisenatide. They are indicated for the treatment of type 2 diabetes mellitus as adjunct therapy to diet and exercise.[35-39] GLP-1 RAs (incretin mimetics) stimulate glucose-dependent insulin secretion (responding to elevated glucose, thus reducing fasting and postprandial glucose as well as glycated hemoglobin, A1c), suppress glucagon release (reducing hepatic glucose output), and delay gastric emptying (decreasing meal-associated glucose excursions).[32,33] These agents are associated with a relatively low risk of hypoglycemia because

of their glucose-dependent nature.[33] In clinical trials, GLP-1 RAs have been shown to increase risks of hypoglycemia only when used with sulfonylureas and insulin.[34] All GLP-1 RAs are subcutaneous injectables, and, thus, they might pose some resistance and barriers in those who have needle-phobia.

Contraindications and Warnings

As summarized in Table 4, all GLP-1 RAs carry a boxed warning, indicating the risk of thyroid C-cell tumors.[35-39] This class of medications is contraindicated for patients who have a personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2.[35-39] Thus, it is imperative to discuss personal and family histories before starting anyone on a GLP-1 RA. No special prescreening is needed other than a history and physical exam that includes a thyroid exam.

There have been postmarketing case reports of patients developing pancreatitis while taking GLP-1 RAs. As a result, the FDA has recommended a warning of the association of pancreatitis with the use of these agents. Although the FDA's recent review stated these agents did not appear to have a causal link with pancreatitis, the FDA recommends continued surveillance and discontinuation of the agent if a patient develops pancreatitis.[35-39] Other less severe side effects for GLP-1 RAs include nausea, vomiting, diarrhea, and dyspepsia due to their effect on slowing gastric emptying. However, weight loss with these agents is not tied to side effects (weight reduction of 0.4-2.9 kg in GLP-1 RA monotherapy trials).[35-39]

In terms of efficacy, monotherapy trials of GLP-1 RAs have shown that they reduced A1c between 0.7% and 1.6%, as summarized in Table 4. Their impact on fasting serum glucose reduction was shown to be between 16 mg/dL and 29 mg/dL.[35-39]

Exenatide ER, dulaglutide, and albiglutide have once-weekly dosing; exenatide IR has twice-daily dosing; and liraglutide and lixisenatide are dosed once daily.[35-39] No renal or hepatic dose adjustment is recommended for liraglutide, dulaglutide, and albiglutide. Since exenatide is cleared via the kidneys, exenatide is not recommended if creatinine clearance (CrCl) is < 30 mL/min,[35-39] but hepatic impairment would not affect blood concentration of this agent.[35,36] There are no adequate and well-controlled clinical trials in pregnant women, so GLP-1 RAs have pregnancy category C rating.[35-39]

Key Studies/Trials

Recently, the LEADER trial showed that liraglutide provided a cardiovascular benefit in patients at risk for myocardial infarction and stroke in a trial with time-to-event analysis.[40] The rate of mortality (first occurrence) in type 2 diabetic patients from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was lower (hazard ratio, 0.87; 95% confidence interval, 0.78-0.97), suggesting a cardioprotective property.[40] To date, no other GLP-1 RAs have clinical trials with conclusive evidence determining their macrovascular risk reduction capacity.

The cost is approximately $500 to $700 per month.[13]

Practical Considerations

GLP-1 RAs have been effective tools in the treatment of type 2 diabetes. They address a number of pathophysiologic problems, including glucagon suppression, hepatic glucose production, increase in satiety, and glucose-dependent insulin secretion. They are excellent medications to add to other agents. In fact, they can be added to any class of medications, except DPP-4 inhibitors.

GLP-1 RAs are all injections, but the benefit of weight loss has demonstrated that "injection resistance" may be much less than once thought. Many patients are willing to try injectable therapy when the medication is associated with weight loss and lower rates of hypoglycemia. These agents slow the gastrointestinal (GI) tract and may worsen gastroparesis. In fact, if the patient has significant GI bloating and early satiety, it may signal that the patient has gastroparesis.

The selection between these agents is based largely on patient preference. The short-acting exenatide IR addresses the postprandial glucose more than other agents but also has a slightly smaller reduction in fasting glucose and A1c. The data for the new short-acting GLP-1 RA lixisenatide appear to be similar.

The selection between long-acting agents depends on what works best for the patient's schedule and the skills for preparing the pen device. Liraglutide is given once daily any time of the day. The pen device needs no preparation. The pen dials to all three FDA-approved devices, and titration is recommended to get to the maximum dose. The once-weekly GLP-1 RAs include dulaglutide, albiglutide, and exenatide ER. The dulaglutide pen needs no special medication mixing and has a retractable needle that may make it favorable for those who are nervous about injections. It is important to hold the device to the skin long enough for the "two clicks" that allow the needle to advance and retract. Albiglutide and exenatide weekly need to have the medication suspended before administration.

Dipeptidyl Peptidase-4 Inhibitors

Therapeutic/Clinical Indications

The other agents that use the "incretin effect" are dipeptidyl peptidase-4 (DPP-4) inhibitors. These oral agents work to prolong the levels of endogenous GIP and GLP-1 in the body circulation. Normally, when GIP and GLP-1 are released in response to a meal, the DPP-4 polypeptides degrade GIP and GLP-1 within minutes. Inhibiting the degradation of these incretins increases their effects on first-phase insulin secretion and glucagon inhibition.[31] DPP-4 inhibitors are sitagliptin, saxagliptin, linagliptin, and alogliptin. Like GLP-1 RAs, the DPP-4 inhibitors also exert glucose-dependent insulin secretion with a relatively low risk of hypoglycemia when used alone. By mildly reducing the breakdown of GLP-1 and GIP, these agents not only mildly raise these hormones' levels and have a mild glucose-lowering effect but also cause few side effects.

When DPP-4 inhibitors are used with either sulfonylurea or insulin, the risk of hypoglycemia can increase. If combination therapy is needed with these agents,

Table 5. Key Characteristics of Commercially Available DPP-4 Inhibitors[43-46]

	Sitagliptin[43]	Saxagliptin[44]	Linagliptin[45]	Alogliptin[46]
Contraindications	Serious hypersensitivity reaction to DPP-4 inhibitors			
Common Side Effects (> 5% of patients)	Upper respiratory tract infection Nasopharyngitis Headache	Upper respiratory tract infection Urinary tract infection Headache Peripheral edema (in combination with TZD)	Nasopharyngitis	Nasopharyngitis Headache Upper respiratory tract infection
Warnings & Precautions	Post-marketing reports of acute pancreatitis (including fatal pancreatitis) Severe and disabling arthralgia			
Strengths	100, 50, 25 mg tablets	5, 2.5 mg tablets	5 mg tablet	25, 12.5, 6.25 mg tablets
Mean A1c Reduction (%)*	Placebo: +0.2 100 mg: -0.6 (At Week 24)	Placebo: +0.2 5 mg: -0.5 2.5 mg: -0.4 (At Week 24)	Placebo: +0.3 5 mg: -0.4 (At Week 24)	Placebo: 0 25 mg: -0.6 (At Week 26)
Mean Fasting Serum Glucose Reduction (mg/dL)*	Placebo: +5 100 mg: -12 (At Week 24)	Placebo: +6 5 mg: -9 2.5 mg: -15 (At Week 24)	Placebo: +15 5 mg: -9 (At Week 24)	Placebo: +11 25 mg: -16 (At Week 26)
2-hour Post-Prandial Glucose Reduction (mg/dL)*	Placebo: -2 100 mg: -49 (At Week 24)	Placebo: -6 5 mg: -43 2.5 mg: -45 (At Week 24)	Placebo: +25 5 mg: -34 (At Week 24)	Not available
Dosing	Once daily			

* In trials used as monotherapy; changes from baseline
** CrCl = Creatinine clearance

consider reducing the dose of sulfonylurea or insulin to prevent episodes of hypoglycemia.[43-46] Compared to GLP-1 RAs with a six- to 10-fold increase in GLP-1 levels, DPP-4 inhibitors only modestly increase GLP-1 levels by two- to three-fold (although they still increase GIP levels), leading to minimal to no effect on slowing gastric emptying.[41,42] Unlike GLP-1 RAs, DPP-4 inhibitors do not affect body weight, appetite, or satiety; therefore, these agents are considered weight neutral.[31]

As summarized in Table 5, DPP-4 inhibitors are contraindicated only if patients have severe hypersensitivity to the active ingredients.[43-46] The most common side effect for these agents is upper respiratory infection, and there was higher incidence of peripheral edema when saxagliptin was used with TZD.[43-46] In 2015, the FDA issued a warning stating that DPP-4 inhibitors may cause severe joint pain.[47] In addition, acute pancreatitis has been revealed in post-marketing data for all agents in this class.[43,45,46,55] The FDA was unable to conclude that these agents raised the risk of pancreatitis any greater than the risk from type 2 diabetes alone. Despite this, DDP-4 inhibitors are not recommended in patients with a history of pancreatitis or those with substantially known pancreatitis risk from other causes, such as extensive alcohol intake or severe hypertriglyceridemia.

In monotherapy trials comparing DPP-4 inhibitors with placebo, average A1c reduction for these agents was between 0.4% and 0.6%.[43-46] Although average fasting serum glucose reduction was between 9 and 16 mg/dL, two-hour postprandial glucose reduction was between 34 and 49 mg/dL (data were not available for alogliptin).[43-46] Efficacy for specific agents can be found in Table 5.

DPP-4 inhibitors are once-daily dosing. All of these agents require dose adjustments in renal-impaired patients (with the exception of linagliptin).[43-46] There is no hepatic dose adjustment recommended for these medications.[43-46] Since results on safe use in pregnancy have been established in animals but not in pregnant women, DPP-4 inhibitors have been classified as pregnancy category B.[43-46]

Key Studies/Trials

In the TECOS trial (a randomized, double-blind study including 14,671 patients), sitagliptin was not associated with any adverse cardiovascular outcomes, including hospitalization for heart failure, when added to patients' existing therapies.[48] The cardiovascular outcome trial for saxagliptin, SAVOR-TIMI 53, showed that although saxagliptin had no effect on the rate of ischemic events, cases of heart failure leading to hospitalization happened slightly more frequently in the saxagliptin arm in the two-year Kaplan-Meier model.[49] The EXAMINE trial, involving alogliptin, showed that there was no increased rate of adverse cardiovascular events in type 2 diabetic

patients who had a history of acute coronary syndrome.[50] Results for linagliptin cardiovascular outcome trial (CAROLINA®) are not yet available.

The cost is approximately $400 for 30 tablets.[13]

Practical Considerations

DPP-4 inhibitors have had widespread use in the United States. These agents are attractive in that they are oral and once daily. Another key feature for DDP-4 inhibitors is that they are the only class of diabetes medications for which it is recommended to start with the maximum dose. The therapeutic dose is the maximum dose, and the dose should be reduced only when there is renal impairment (sitagliptin, saxagliptin, and alogliptin). Linagliptin is not cleared through the kidneys, so no renal dosing is necessary. Compared to other classes of medications, these agents have moderate A1c reductions (0.4%-0.7%). They can be added to any class of medications with the exception of the GLP-1 RAs. However, one warning warrants repeating: When glucose-dependent insulin secretion agents are paired with glucose-independent agents, the lower risk of hypoglycemia is negated. Caution should be used when the DPP-4 inhibitors are paired with sulfonylureas, meglitinides, and insulin.

One area in which DPP-4 inhibitors may have an edge is in the elderly who are prone to hypoglycemia. Often, the A1c goal in the elderly is loosened to reduce the risk of hypoglycemia. DPP-4 inhibitors, alone or with a basal insulin, may be a good selection for elderly community dwellers, those in extended care facilities, and possibly hospitalized patients.

Amylin Analog

Amylin and insulin are co-manufactured and released by pancreatic beta cells in response to food consumption. In healthy individuals, they exhibit similar physiological patterns (fasting and postprandial) and serve as cofactors to reduce the postprandial excursions seen with meals. The only agent in this class is pramlintide, which is indicated for type 1 and 2 diabetes as an adjunct therapy to mealtime insulin.[51] Since pramlintide is an amylinomimetic agent, it functions by slowing gastric emptying, limiting glucagon secretion postprandially (suppresses hepatic glucose output), and inducing satiety (results in reduction of caloric intake and possibly weight loss).[51]

Table 6. Efficacy of Pramlintide[51]

	Type 2 Diabetes (pramlintide 120 mcg)	Type 1 Diabetes (pramlintide 30 or 60 mcg)
A1c Change from Baseline	120 mcg: -0.57% Placebo: -0.17% (at month 6)	30 or 60 mcg: -0.43% Placebo: -0.10% (at month 6)
Weight Change from Baseline	120 mcg: -1.5 kg Placebo: +0.2 kg (at month 6)	30 or 60 mcg: -1.1 kg Placebo: +0.6 kg (at month 6)
Percent Change in Insulin Doses (Rapid/Short-Acting)	120 mcg: -3.0% Placebo: +6.5% (at month 6)	30 or 60 mcg: -3.6% Placebo: +1.7% (at month 6)
Percent Change in Insulin Doses (Long-Acting)	120 mcg: -0.2% Placebo: +5.2% (at month 6)	30 or 60 mcg: +1.9% Placebo: +2.5% (at month 6)

Pramlintide is administered by injection before meals. It can be administered concurrently with mealtime insulin but is not indicated to mix into a single injection. Although this can stimulate insulin secretion and lead to satiety and weight loss, it has not gained much popularity, as it requires the person to double the number of injections per day. If a patient eats three meals per day, he or she will need six injections: three pramlintide and three mealtime insulin doses. Also, the gastrointestinal side effects of nausea and bloating are problematic for some patients. It is recommended that people reduce the dose of mealtime insulin by 50% when starting pramlintide, but often the dose will need to be adjusted multiple times to maintain the optimal glucose reduction without hypoglycemia.

Contraindications and Warnings

A boxed warning has been issued for pramlintide, noting an increased risk of insulin-induced severe hypoglycemia (usually occuring within three hours after a pramlintide injection), especially in patients with type 1 diabetes.[51] This agent is contraindicated in patients who are allergic to the active ingredient and metacresol, who have been diagnosed with gastroparesis, and who have hypoglycemia unawareness.[51] The most common adverse reactions (≥ 5% incidence) in both types 1 and 2 diabetic patients include nausea, anorexia, vomiting, and fatigue.[51] The efficacy profile for pramlintide is summarized in Table 6.

As indicated in Table 6, the recommended dose for type 1 diabetes is either 30 mcg or 60 mcg injected immediately before a major meal; whereas for type 2 diabetes, the recommended dose is an injection of 120 mcg before a major meal.[51] No renal-dose adjustment is needed for those with moderate or severe renal impairment having creatinine clearance > 20 mL/min to ≤ 50 mL/min; in addition, blood concentration of pramlintide is not affected by hepatic dysfunction because of its renal metabolism.[51] Pramlintide is a pregnancy category C drug with no adequate studies conducted in pregnant women.[51]

The cost is approximately $1,500 for 2 pens.[13]

Practical Considerations

Although this injectable agent is attractive to some because of the potential for weight loss, the side effects and injection frequency have limited its use. If this agent could be co-formulated with insulin (as our bodies produce it), it may be a much more attractive option. One area in which it has been used in the authors' practice is in adolescents with type 1 diabetes who are gaining

Table 7. Efficacy of Bromocriptine as Monotherapy in Type 2 Diabetes Patients[52]

A1c Change from Baseline (at Week 24)	Bromocriptine 1.6 – 4.8 mg: - 0.1% Placebo: +0.3%
Fasting Plasma Glucose (mg/dL) Change from Baseline (at Week 24)	Bromocriptine 1.6 – 4.8 mg: 0 Placebo: +23

weight on insulin. These patients already are accustomed to many injections per day; insulin resistance is very high during puberty, which may make pramlintide a good option for some patients.

Dopamine Receptor Agonists

Bromocriptine, a sympatholytic D2-dopamine receptor agonist, has been approved for the treatment of type 2 diabetes mellitus since 1978,[52,53] and its efficacy and safety in type 2 diabetes patients was supported by a recent review.[54] Administration of bromocriptine within two hours of awakening has been hypothesized to supplement the low dopamine levels in hypothalamus.[53] In addition, bromocriptine reduces sympathetic tone within the central nervous system, leading to a possible reduction of fasting plasma glucose levels as a result of suppressed hepatic glucose output.[53] The exact mechanism of action is still unknown.

Several contraindications have been identified: hypersensitivity to ergot-related drugs, syncopal migraines (due to precipitation of orthostatic hypotension), and nursing women (postmarketing reports of stroke in this subpopulation).[52] Because of the risk of orthostatic hypotension, patients who have been on antihypertensive medications are advised to use bromocriptine cautiously, and orthostatic vital signs should be assessed prior to initiation and periodically thereafter.[52] Exacerbation of psychotic disorders or reduction in effectiveness of antipsychotics is also a concern; thus, bromocriptine is not recommended in patients with severe psychotic disorders.[52] The efficacy profile for bromocriptine is summarized in Table 7.

The cost of bromocriptine is approximately $450 for 120 tablets.[13]

Contraindications and Warnings

Because of its effect on blood pressure, the initial dose of bromocriptine is 0.8 mg daily, which can be titrated weekly by 0.8 mg to a maximal tolerated daily dose of 1.6 to 4.8 mg.[52] Bromocriptine should be taken with food two hours after waking in the morning.[52] Since bromocriptine is metabolized predominantly by the liver, patients with hepatic impairment should use it cautiously; renal dose adjustment has not been established because kidney elimination of bromocriptine is rather limited and no pharmacokinetic studies have been conducted (recommended to use cautiously in renally impaired patients).[52] Bromocriptine has been categorized as pregnancy category B.[52] No data are available for safety in breastfeeding.

Practical Considerations

Bromocriptine as a single daily-dose oral medication with a novel mechanism of action has promise. This medication is most effective when used within two hours of waking. However, use of the medication has been very limited. This is likely to be related to the cost and only mild efficacy. There also may be concern about side effects of this medication. The endocrine community has used this medication for years to treat pituitary adenomas.

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CME Questions

1. Which of the following statements is ***false*** regarding to GLP-1 receptor agonists?
   a. GLP-1 receptor agonists cause a relatively low risk of hypoglycemia due to their glucose-dependent nature.
   b. GLP-1 receptor agonists manage type 2 diabetes mellitus through suppressing insulin secretion, increasing glucagon release, and delaying gastric emptying.
   c. GLP-1 receptor agonists are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome type 2.
   d. Liraglutide, dulaglutide, and albiglutide do not have renal dose adjustments recommended by manufacturers when patients' CrCl < 30 mL/minute.
2. Which of the following pairs of information regarding DPP-4 inhibitors is ***false***?
   a. Linagliptin: no dose adjustment is needed for renal-impaired patients
   b. DPP-4 inhibitors: pregnancy category B
   c. Sitagliptin with TZD: higher incidence of peripheral edema
   d. DPP-4 inhibitors: post-marketing surveillance showed some patients had developed severe joint pain and acute pancreatitis being on these agents
3. Which medication demonstrated cardiovascular benefits in clinical trials?
   a. Glyburide
   b. Saxagliptin
   c. Empagliflozin
   d. Sitagliptin
4. What class of medications is contraindicated in symptomatic heart failure?
   a. SGLT2 inhibitors
   b. Alpha glucosidase inhibitors
   c. GLP-1 agonist
   d. Thiazolidinediones

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