Navigating *the role of* Family Medicine *in the* Modern Treatment *of* Type 2 Diabetes

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CME INFORMATION

Target Audience

This activity is intended for family medicine practitioners, including physicians, physician assistants, nurse practitioners and nurses who manage patients with type 2 diabetes.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Describe the mechanism of action of current glucagon-like peptide-1 receptor agonists (GLP-1 RAs)
- Review current efficacy, safety and tolerability data on GLP-1 RAs, and differences between available and emerging agents
- Discuss the potential long-term benefits of treatment with a GLP-1 RA
- Review data on the use of GLP-1 RAs in combination with basal insulin and other antihyperglycemic medications
- Employ strategies to customize combination therapy with GLP-1 RAs and other antihyperglycemic therapies

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Dear Colleague:

Diabetes and its associated complications represent an increasing health care burden. Estimated health care costs for individuals diagnosed with diabetes are approximately 2.3 times higher than those for individuals without diabetes.[1] Despite growing awareness of the importance of glycemic control and of optimal management of risk factors, many patients with diabetes are not achieving their treatment goals.[2]

Meanwhile, the breadth and number of treatment options for diabetes, and especially for type 2 diabetes, are expanding rapidly. Advances in treatment create opportunities to improve outcomes with more personalized treatment plans. However, these advances may also make treatment selection and planning more complex. As treatment evolves to include a variety of agents, which can be used alone and in combination with other therapies, self-management remains a critical component of successful treatment.

Family medicine practitioners are uniquely positioned to support self-management and to address all aspects of diabetes care. At the recent 2017 Family Medicine Experience (FMX), we had the honor of speaking at a symposium about the role of family medicine in the treatment of type 2 diabetes. We discussed some of the latest advances in treatment, along with strategies to overcome challenges in designing and tailoring individualized treatment plans. With this publication, we are pleased to share some of the material that was presented, along with key insights from our discussion.

Thank you for your interest, and we hope this information is helpful in the care of your patients with type 2 diabetes.

Sincerely,

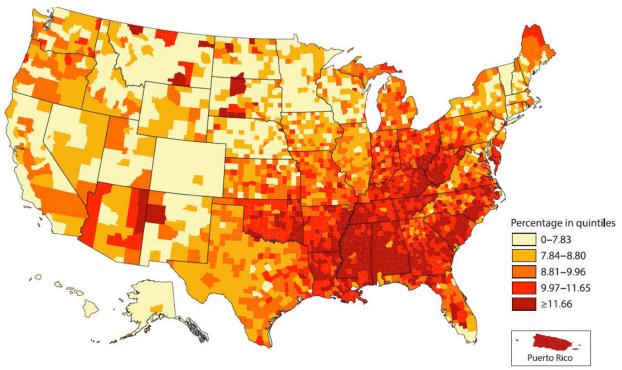
Jeff Unger, MD, FAAFP, FACE **Mark W. Stolar, MD**

SCOPE OF THE ISSUE

The prevalence of diabetes is escalating.

In the United States, almost 10% of the population has diabetes, almost all of which is type 2 diabetes mellitus (T2DM; Figure 1).[3] About 1 in 4 people with diabetes remains undiagnosed.[3] An estimated 84.1 million adults in the US (representing 1/3 of adults) had prediabetes in 2015.[3] Individuals with fasting plasma glucose levels between 100 and 125 mg/dL and glycated hemoglobin (HbA1c) values between 5.7% and 6.4% are considered to have prediabetes.[3]

Figure 1: 2013 Diagnosed Diabetes Prevalence[3]



By the year 2050, the prevalence of total diabetes, both diagnosed and undiagnosed, is projected to increase from 1 in 10 US adults to between 1 in 5 and 1 in 3 adults.[4] The annual incidence of new cases of diagnosed diabetes is projected to increase from 8 cases per 1000 in 2008 to approximately 15 cases per 1000 by the year 2050.[4] The projected increases are largely attributed to three key demographic factors: the aging of the US population; an increasing size of higher-risk minority populations; and declining mortality among people with diabetes.[4]

IMPORTANCE OF GLYCEMIC CONTROL

Uncontrolled hyperglycemia can lead to diabetes-related complications.[2]

Findings from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that lowering HbA1c reduces the risk of diabetes-related complications.[5] In patients with HbA1c >6%, every 1% decrease in HbA1c resulted in a 21% decrease in the risk of any diabetes-related endpoint, a 14% decrease in the risk of myocardial infarction, a 12% decrease in the risk of stroke, and a 37% decrease in the risk of microvascular complications.[5] There is no threshold of HbA1c below which the benefits of reduced complications are not seen.[5] Results from this study highlight the importance of achieving tight glycemic control in the management of diabetes.[5]

Delayed intervention due to "clinical inertia" in patients with type 2 diabetes can have real consequences.

The impact of delayed versus timely intensification of therapy on cardiovascular outcomes was evaluated in a retrospective cohort study of more than 100,000 patients newly diagnosed with T2DM in the United Kingdom. Within 2 years of being diagnosed with T2DM, 26% of patients who still had HbA1c levels above 7% did not receive additional treatment to address their hyperglycemia.[6] After 5.3 years, the patients who did not receive therapy intensification when necessary had a 67% higher risk of having a myocardial infarction, 64% higher risk of having a stroke, and 62% higher risk of a composite cardiovascular event compared with those patients receiving timely intensification.[6]

MEDICATION ADHERENCE IN TYPE 2 DIABETES

One significant factor involved in outcomes of patients with T2DM is the extent to which they are adherent to and persistent with their medication regimen.[7] To quantify the relationship between outcomes and adherence, a blinded examination of 26 million insurance claims, representing 1.4 million insured individuals, was conducted.[8] Patients who were adherent to their oral diabetes medications had 235 fewer emergency department visits and 50 fewer inpatient hospitalizations per 1000 patients compared with patients who were nonadherent.[8]

Rates of medication adherence vary widely in the literature, with anywhere between 38.5% and 93.1% of patients classified as adherent.[9] A 2015 meta-analysis used 27 published studies to explore the link between medication type (oral administration +/- insulin) and adherence.[9] This systematic review showed that depression and high cost of health care were consistently associated with poor medication adherence.[9] An analysis of electronic prescriptions in Massachusetts showed that 31% of new diabetes prescriptions for adults were never filled.[10]

The data paint a sobering picture of the future growth of diabetes.

A retrospective adherence analysis, relying on commercial and Medicare Supplemental health insurance claims databases, examined data from more than 200,000 patients who were prescribed an oral antihyperglycemic drug.[7] Within 1 year of starting a new diabetes therapy, many patients discontinued the medication and switched to a new medication or remained off of any antidiabetic medication.[7] Different classes of antidiabetes medications showed different rates of discontinuation: >41% of patients discontinued a dipeptidyl peptidase-4 inhibitor (DPP-4i); 48% of patients discontinued a sulfonylurea (SU); and 51% discontinued a thiazolidinedione (TZD).[7]

Improving adherence

The following factors have been associated with improved medication adherence in patients with T2DM[13,14]:

- Medications with fewer adverse events
- Reduced treatment complexity
- Patient education and increased knowledge
- Medications benefits outweigh medication costs
- Improved continuity of care and increased provider communication

ADHERENCE
is defined as the extent to which patients take medications as prescribed by their health care providers.[11]

PERSISTENCE
is defined as the ability of a person to continue taking medications for the intended course of therapy.[12]

CLINICAL PRACTICE GUIDELINES[2,15]

The American Diabetes Association and the American Association of Clinical Endocrinologists/ American College of Endocrinology have developed clinical practice guidelines for the management of patients with diabetes, including T2DM. Both of these guidelines can and should be used by family medicine clinicians as a practical guide to evidence-based approaches to treatment, while they take into consideration the whole patient, including the spectrum of risks and complications.

Lifestyle optimization, emphasizing daily physical activity and healthy eating, is a first step in diabetes management and should remain in place throughout the patient's life. Pharmacotherapy can be initiated in conjunction with lifestyle management and should be seen as an adjunct, not as the next step after a failure. Weight loss should be considered in all appropriate patients with prediabetes or T2DM.

The goal for many patients without other serious illness and at low risk of hypoglycemia is an HbA1c level ≤6.5%. Less stringent goals for HbA1c (eg, <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite numerous strategies.

Both guidelines have algorithms that outline when and how to initiate pharmacotherapy in patients with T2DM. In all cases, the guidelines state that if the patient has not achieved the HbA1c target within 3 months of initiating a particular therapy, then therapy should be intensified (by adding another agent or by adding insulin).

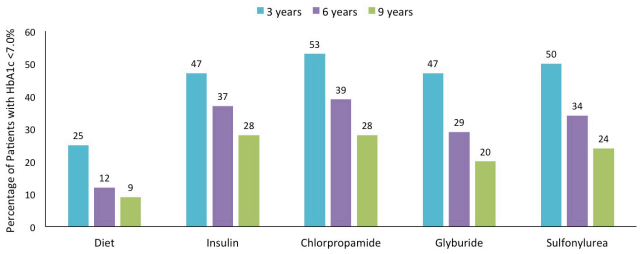
PROGRESSION OF DIABETES

Given that the progression of diabetes often manifests as increasing blood glucose levels over time, most patients with T2DM will eventually need combination therapy to manage their disease. As time elapses after initiating therapy, the proportion of patients with T2DM achieving their HbA1c target decreases. For instance, in UKPDS patients receiving sulfonylurea therapy, 50% achieved HbA1c <7% at 3 years, 34% achieved it at 6 years, and 24% achieved it at 9 years (Figure 2).[16] Similarly, a separate study, in which monotherapy failure was defined as fasting plasma glucose levels >180 mg/dL on consecutive testing after at least 6 weeks of treatment, found that the likelihood of monotherapy failure increased with time after initiating therapy.[17]

In the natural progression of T2DM, insulin resistance and deficits in insulin secretion are thought to be key factors leading to hyperglycemia.[18] In response to insulin resistance, ß-cells secrete more insulin, and this will initially increase insulin levels to compensate.[18] However, ß-cell function starts to deteriorate in prediabetes and is significantly reduced by the time diabetes is diagnosed (Figure 3).[18]

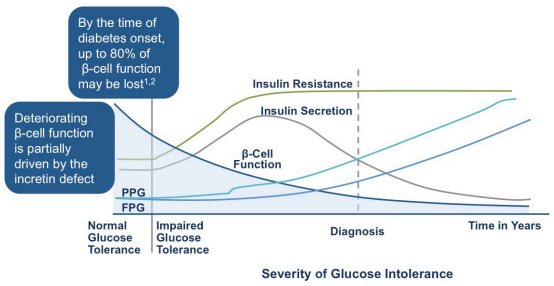
Escalate therapy if HbA1c target is not achieved within 3 months.

Figure 2: Patients with T2DM who received monotherapy had decreasing rates of reaching HbA1c levels less than 7.0% with increasing duration of monotherapy.[16]



Incretin hormones, which modulate insulin release from the pancreas after a meal, also play a role in the progression of T2DM. When food enters the gastrointestinal tract, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are released from enteroendocrine cells into the circulation.[19] The release of these incretins produces blood insulin levels that are up to 50% higher than the levels achieved after an intravenous glucose infusion.[19,20] The elevated insulin response provided by incretins is known as the "incretin effect." The incretin effect is reduced in patients with T2DM and plays an important role in progressive ß-cell failure.[18] GLP-1 is a key player in the incretin effect.[21]

Figure 3: Progressive ß-cell dysfunction is a key driver of progressive dysglycemia in T2DM.[18]



PPG, postprandial plasma glucose; FPG, fasting plasma glucose.

What is GLP-1?

Upon food ingestion, GLP-1 is secreted into the circulation from L cells of the small intestine.[22] GLP-1 increases the ß-cell response by enhancing glucose-dependent insulin secretion.[23] GLP-1 decreases ß-cell workload and, hence, the demand for insulin secretion by several mechanisms.[23] It regulates the rate of gastric emptying such that meal nutrients are delivered to the small intestine and, in turn, absorbed into the circulation more smoothly, reducing peak nutrient absorption and insulin demand (ß-cell workload).[23] GLP-1 also decreases postprandial glucagon secretion from pancreatic ß-cells in a glucose-dependent manner, which helps to maintain the counterregulatory balance between insulin and glucagon.[23] By decreasing glucagon secretion, GLP-1 has an indirect benefit on ß-cell workload because increasing the ratio of insulin to glucagon leads to decreased hepatic glucose output.[24]

GLP-1 also affects the central nervous system, resulting in increased satiety (sensation of satisfaction with food intake) and a reduced food intake.[25] By decreasing ß-cell workload and improving ß-cell response, GLP-1 is an important regulator of glucose homeostasis.

In T2DM, there is a deficiency of GLP-1, which worsens progressively with the natural progression of the disease.[21] In addition, GLP-1 has less of a stimulatory effect on insulin secretion.[21]

GLP-1 RECEPTOR AGONISTS (GLP-1 RAs)

Owing to its effects on glucose homeostasis, GLP-1 has become an attractive target for diabetes pharmacotherapy. However, the GLP-1 peptide itself has a short half-life, as it is rapidly inactivated by the enzyme DPP-4.[26] Therefore, other strategies have been employed to enhance GLP-1 activity, including the use of GLP-1 RAs.[26]

GLP-1 RAs are a group of peptides that are structurally similar to native GLP-1 and activate the GLP-1 receptor.[26] The peptides have chemical modifications that confer more biological stability than GLP-1, and the type of modificationdetermines much of the pharmacokinetic properties.[26] Generally speaking, GLP-1 RAs are divided into two categories: shorter-acting and longer-acting agents (Table 1).[26,27]

Currently there are 5 drugs in 6 formulations available in the US. All of the approved drugs are administered by subcutaneous injection. They differ in the dosing frequency and duration of action. Other GLP-1 RAs with different administration routes are in clinical trials (Table 2).

The most common adverse event associated with GLP-1 RAs is nausea, affecting 25% to 60% of treated patients.[26] Nausea is generally moderate or mild in severity and related to treatment frequency.[28] Gastrointestinal discomfort and nausea generally subside as GLP-1 RA treatment continues.[28,29] Other common adverse events are vomiting and diarrhea.[26] In clinical trials, discontinuation rates due to adverse events were low overall, with less than 10% of patients in the clinical trials of GLP-1 RAs discontinuing due to treatment-related adverse events.[30] Acute

Table 1. Shorter Acting and Longer Acting GLP-1 RAs

	Shorter Acting	Longer Acting
Compounds	Exenatide BID, lixisenatide	Albiglutide, dulaglutide, exenatide QW, liraglutide, semaglutide*
Half-life	2-5 hours	12 hours to several days
Effects		
FPG reduction	Modest	Strong
Postprandial hyperglycemia reduction	Strong	Modest
Fasting insulin secretion stimulation	Modest	Strong
Glucagon secretion	Reduction	Reduction
Weight reduction	Yes	Yes
Potential for nausea	Yes	Yes

*Not approved by the FDA for use in the US. Table modified from Fonseca VA. *Clin Ther.* 2014; and Meier JJ. *Nat Rev Endocrinol.* 2012.[26,27]
FPG, fasting plasma glucose

Table 2. GLP-1 RA Formulations

Drug	Dose	FDA Approval
Exenatide (Byetta®)	5–10 mcg BID	2005
Exenatide (Bydureon®)	2 mg once weekly	2012
Liraglutide (Victoza®)	1.2–1.8 mg QD	2010
Albiglutide (Tanzeum®)	30-50 mg once weekly	2014
Dulaglutide (Trulicity®)	0.75–1.5 mg once weekly	2014
Lixisenatide (Adlyxin®)	10–20 mcg QD	2017
Semaglutide	once weekly, oral and injectable	Investigational
Exenatide implantable osmotic pump (ITCA 650)	5 minute insertion procedure in office, lasts 3–6 months	Investigational

pancreatitis has been reported in clinical practice with GLP-1 RA treatment, though the evidence is equivocal as to a true association between the two.[26]

Most GLP-1 RAs, except exenatide short-acting formulation and lixisenatide, are contraindicated in persons with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.[31-34] All GLP-1 RAs, except exenatide short-acting formulation and lixisenatide, carry a black box warning of an increased risk of thyroid tumors, which was shown in animal models.[30-33]

Patients taking GLP-1 RAs should be monitored for fasting blood glucose, HbA1c, serum creatinine, and blood urea nitrogen (BUN). GLP-1 RAs may interact with other agents that induce hypoglycemia and may reduce the rate of absorption of orally administered drugs.[31-36]

Where do GLP-1 RAs fit in T2DM therapy?

According to the ADA Standards of Care in Diabetes and the AACE/ACE Consensus Statement, GLP-1 RAs can be used as one of the agents in dual or triple therapy, including in combination with insulin.[2,15] The AACE/ACE Consensus Statement also includes GLP-1 RAs as a possible monotherapy for patients with T2DM.[15]

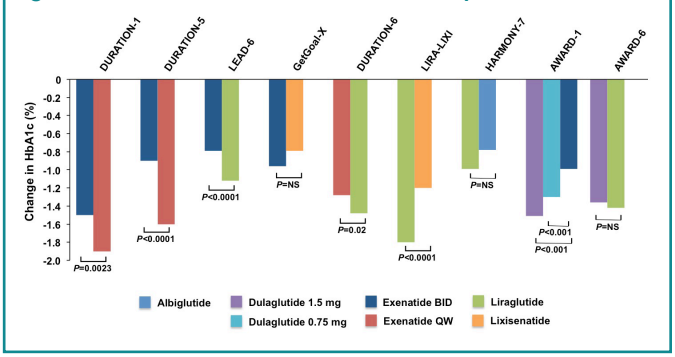
The choice of using GLP-1 RA therapy for patients with T2DM should be made on the basis of patient preference, disease characteristics, drug efficacy, and adverse events, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia.[2]

Metabolic outcomes of GLP-1 RA clinical trials

In head-to-head comparisons, all available GLP-1 RAs reduced HbA1c levels from baseline by an average of about 1 to 1.5%, with longer-acting agents generally producing greater reductions than shorter-acting agents. Although the reduction in HbA1c was more pronounced with liraglutide than with albiglutide, the predefined noninferiority criteria were not met. Liraglutide and dulaglutide produced very similar effects (Figure 4).[30,37]

Patients receiving GLP-1 RAs also showed weight loss in clinical trials, with few significant differences between agents.[30,37] The weight loss associated with GLP-1 RA therapy appears to be greater than that seen with DPP-4 inhibition, as shown in a study comparing the effects of dulaglutide with those of sitagliptin. After 52 weeks, patients receiving dulaglutide had lost up to approximately 3 kg of body weight, while patients receiving sitagliptin had lost about 1.5 kg.[38] An analysis of patients receiving exenatide short-acting formulation showed that the reduction in body weight was

Figure 4: GLP-1 RA treatment reduces HbA1c by 0.8 – 1.9%.[30, 37]



NS, not significant

unlikely to be driven by the direct effect of nausea.[39]

When GLP-1 RAs were combined with metformin therapy, the percent of patients that experienced one severe hypoglycemia event was between 1.3% and 5.6%.[31-36] When GLP-1 RAs were combined with basal insulin, the proportion of patients experiencing hypoglycemia was between 16% and 35.3%.[31-36]

Cardiovascular outcomes in GLP-1 RA clinical trials

Hypoglycemia causes physiological abnormalities that may increase the risk for cardiovascular events in patients with diabetes.[40] Therefore, there is interest in emerging data on cardiovascular outcomes in patients treated with GLP-1 RAs. In the randomized, placebo-controlled study of liraglutide 1.8 mg QD, patients receiving liraglutide had a 13% lower rate of the composite cardiovascular outcome (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction [MI], or nonfatal stroke) than patients receiving placebo.[41] In a randomized, placebo-controlled study, patients receiving semaglutide showed a 26% lower rate of the composite cardiovascular outcome.[42] When evaluated in high-risk patients with T2DM and recent acute coronary syndrome, lixisenatide showed no increased risk for cardiovascular death, MI, stroke, unstable angina, or heart failure compared with placebo.[43] Similar findings were recently reported in a study evaluating the cardiovascular effects of once-weekly exenatide in patients with T2DM, 73% of whom had previous cardiovascular disease. Over a median follow-up period of 3.2 years, the incidence of major adverse cardiovascular events did not differ significantly between patients who received once-weekly exenatide and those who received placebo.[44] Meanwhile, clinical trials evaluating cardiovascular outcomes in patients treated with other GLP-1 RAs are ongoing.[45]

BARRIERS TO INJECTABLE THERAPY

Family medicine clinicians face multiple challenges in managing a complex disease such as T2DM.[46] Many of the barriers involved in diabetes therapy, including injectable therapy, are due to a lack of knowledge or education.[46] Clinicians may feel that they lack the appropriate knowledge about the pathophysiology of and evidence-based treatments for T2DM, as well as the ability to educate the patient about their disease and medications.[46]

Clinicians may have a baseline assumption about the inability of an average patient with T2DM to handle injectable therapy.[47] There may also be an assumption that the side effects associated with insulin therapy (eg, hypoglycemia and weight gain) carry over to GLP-1 RAs, which is not the case.[47]

Both patients and clinicians may view the move to injectable therapy as a "failure" in the disease management rather than a response to the natural progressive history of T2DM.[47] Fear of injectable therapy, more specifically fear of pain associated with the injections, is common for many patients with T2DM.[47]

How to overcome the barriers?

Clinicians can help patients reduce their fear of injection pain in several ways. Clinicians should reinforce that injection is relatively painless and is performed with a needle that is much thinner than that typically used for vaccinations.[47] Explain that the injections are performed into fatty tissue instead of muscle, which is less painful. Reinforce that injections are easy with the pens available, and consider having a pen on hand for demonstration. Allow the patient to perform a dummy injection where the needle is inserted without injecting the drug. Monitor patients after initiating injectable therapy for their tolerability of the therapy and for use of the correct technique.[47]

GLP-1 RA plus insulin therapy

The use of GLP-1 RA and insulin combination therapy may help patients attain their glycemic goals.[48] These two therapies have complementary actions on the glycemic burden of T2DM.[49]

Basal insulin analogs primarily control nocturnal hyperglycemia and fasting plasma glucose.[49] They are attractive in that they are simple to initiate and carry less risk of hypoglycemia than NPH insulin.[15]

How do you explain GLP-1 RA therapy to a patient?

Here is how Dr. Unger describes GLP-1 RAs at the white board. You can use a drawing on a white board, and the talk takes about 2 minutes.

"When you eat your favorite food, the gut is going to produce a hormone called GLP-1. GLP-1 goes to the pancreas and stimulates the pancreas to produce insulin. That keeps the blood sugar between 80-130. The pancreas also makes glucagon, in the ß-cells, and it is released when blood glucose gets low. Glucagon causes the liver to produce glucose."

"In T2DM, you're not making a lot of insulin or GLP-1 and blood glucose is going up. You're also making a lot of glucagon. We're going to replace some of the GLP-1 that you don't have with a medicine called a GLP-1 receptor agonist. It will go to the pancreas and stimulate the ß-cells to make more insulin, which will lower blood glucose levels back into the normal range and will reduce levels of glucagon. GLP-1 also affects the brain and leads to a feeling of fullness. Watch out for one of the main side effects that is nausea."

In addition to explaining the mechanism of action of GLP-1 RAs, you should also instruct the patient on good injection technique and proper storage of the pen in the refrigerator when not in use. Discuss the possible gastrointestinal disturbances when using GLP-1 RAs, including nausea, vomiting, and diarrhea. Also discuss the signs and symptoms of pancreatitis. Remind patients about the signs of hypoglycemia and what to do if they believe they are experiencing an episode of hypoglycemia.

Educate patients about the importance of adhering to their medication regimen, including GLP-1 RAs. The GLP-1 RA injectable class may pose an even greater adherence challenge. A retrospective study of administrative claims from a US health plan analyzed 1321 patients with T2DM treated with liraglutide once daily.[50] Results showed an adherence rate of 34% (defined as proportion of days covered ≥80%).[50]

GLP-1 RAs have modest to strong effects on both fasting and postprandial plasma glucose.[49] GLP-1 RAs are also simple to initiate and reduce the likelihood of severe hypoglycemia.[49] In clinical practice, the recommended course of action is to add insulin to pre-existing GLP-1 RA therapy. Alternatively, GLP-1 RA therapy may be added to established insulin therapy.[48] The combination of a GLP-1 RA and insulin may be highly effective for optimal glucose control, ameliorating the adverse effects often associated with insulin monotherapy.

Data from clinical studies support the therapeutic potential of GLP-1 RA plus insulin combination therapy, typically showing beneficial effects on glycemic control and body weight, with a low incidence of hypoglycemia, and, in established insulin therapy, facilitating reductions in insulin dose. Clinical studies of GLP-1 RAs added to basal insulin monotherapy therapy versus prandial insulin added to basal insulin therapy showed that adding GLP-1 RAs produced noninferior or significantly superior reductions in HbA1c levels, with a statistically different change in weight (GLP-1 RAs showed weight loss, prandial insulin showed weight gain).[51-55] Reductions in HbA1c levels with GLP-1 RA plus basal insulin ranged between 0.74% and 1.44%, and body weight reductions with GLP-1 RA plus basal insulin were 0.73 kg to 2.8 kg.

Fixed-dose combinations

An emerging area within GLP-1 RA therapy is the availability of fixed-dose combinations of a GLP-1 RA and basal insulin. Currently there are two FDA-approved fixed dose combinations: insulin degludec and of liraglutide in a fixed-dose ratio of 10 units of insulin degludec and 0.36 mg of liraglutide, given subcutaneously once daily; and insulin glargine and lixisenatide in a fixed-dose ratio of 100 units of insulin glargine per mL and 33 mcg of lixisenatide per mL in a 3 mL single-patient use pen.[56,57]

Clinical practicalities of GLP-1 RA plus insulin combination therapy

GLP-1 RAs may be used in combination with basal insulin in patients who do not reach their glycemic target with 2-3 glucose-lowering medications.[1] If the patient is taking a sulfonylurea, consider discontinuing or reducing the dose of SU. If the GLP-1 RA is being added to basal insulin, consider reducing the basal insulin dose 10%–20% if the patient's HbA1c level is ≤7.5%. Thereafter, adjust the basal insulin dose based on self-monitored blood glucose results. With this combination therapy, monitor patients for hypoglycemia.

CONCLUSION

To reduce the progression of T2DM, clinicians should consider pharmacotherapy an adjunct to lifestyle modification. GLP-1 RAs, either alone or combined with insulin, represent useful therapies to help appropriate patients reach their glycemic goals. GLP-1 RAs lower blood glucose by increasing ß-cell secretion of insulin and reducing glucagon production within the pancreatic ß-cells. GLP-RAs also lower HbA1c plasma values, an effect that is enhanced when combined with insulin.[54] This property deserves highlighting, because a reduction in HbA1c level is associated with positive outcomes for patients with T2DM.

KEY COMMENTS AND USEFUL TIPS FROM THE LIVE PRESENTATION

- Insulin does not cause weight gain; food causes weight gain.
- There is nothing better for adherence than success.
- Consider measuring HbA1c levels approximately 4–6 weeks after starting a new therapy to get an early indication of its effectiveness. A lack of change or increase in HbA1c suggests that the patient is not taking the medication as prescribed.
- To put insulin doses in perspective, remember that the average adult without diabetes produces approximately 48 units of insulin daily.
- Diabetes is a multimechanistic disease and there is not one drug that treats every mechanism.
  - Each class of drugs treats one or more mechanisms involved in the development and progression of diabetes, with the exception of sulfonylureas, which do not treat the pathology; they just lower glucose. That is why they fail as a monotherapy, usually within the first 1.5 years.
  - Metformin only affects hepatic glucose production; it does not address ß-cell dysfunction.
- Rather than adding more antihyperglycemic therapies to improve glycemic control, consider discontinuing therapies that are not working.
- The reductions in HbA1c achieved with GLP-1 RAs are more durable over compared with with some other agents such as sulfonylureas.
- Telling patients that a drug may "help" them lose weight is better than saying that the drug will "cause" weight loss.
- Medullary thyroid carcinoma is the only type of thyroid tumor that is a contraindication to the use of several GLP-1 RAs. These drugs are not contraindicated in patients with a family or personal history of papillary or follicular thyroid tumors, which are the more common types.
- A patient who experiences an injection site reaction with one GLP-1 RA may not have a reaction with a different GLP-1 RA, so switching within the class is worth a try.

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REFERENCES

1. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care.* 2013;36(4):1033-1046.
2. American Diabetes Association. Standards of Medical Care In Diabetes–2017. *Diabetes Care.* 2017;40(Supplement 1).
3. National Diabetes Statistics Report, 2017. Centers for Disease Control and Prevention, U.S. Dept. of Health and Human Services.
4. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr.* 2010;8:29.
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258):405-412.
6. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. *Cardiovasc Diabetol.* 2015;14:100.
7. Farr AM, Sheehan JJ, Curkendall SM, Smith DM, Johnston SS, Kalsekar I. Retrospective analysis of long-term adherence to and persistence with DPP-4 inhibitors in US adults with type 2 diabetes mellitus. *Adv Ther.* 2014;31(12):1287-1305.
8. The Diabetes Dilemma: U.S. Trends in diabetes medication use. Express Scripts;2017.
9. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. *Diabet Med.* 2015;32(6):725-737.
10. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. J *Gen Intern Med.* 2010;25(4):284-290.
11. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497.
12. National Council on Patient Information and Education. Enhancing Prescription Medicine Adherence: A National Action Plan. 2007.
13. Garcia-Perez LE, Alvarez M, Dilla T, Gil-Guillen V, Orozco-Beltran D. Adherence to therapies in patients with type 2 diabetes. *Diabetes Ther.* 2013;4(2):175-194.
14. Lokhandwala T, Smith N, Sternhufvud C, Sorstadius E, Lee WC, Mukherjee J. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs. loose-dose combination of oral anti-diabetes drugs. *J Med Econ.* 2016;19(3):203-212.
15. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. *Endocr Pract.* 2017;23(2):207-238.
16. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA.* 1999;281(21):2005-2012.
17. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
18. Kendall DM, Cuddihy RM, Bergenstal RM. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Am J Med.* 2009;122(6 Suppl):S37-50.
19. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev.* 2008;60(4):470-512.
20. Kazafeos K. Incretin effect: GLP-1, GIP, DPP4. *Diabetes Res Clin Pract.* 2011;93 Suppl 1:S32-36.
21. Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes.* 2009;58(4):773-795.
22. Nauck MA, Wollschlager D, Werner J, et al. Effects of subcutaneous glucagon-like peptide 1 (GLP-1 [7-36 amide]) in patients with NIDDM. *Diabetologia.* 1996;39(12):1546-1553.
23. Drucker DJ. Glucagon-like peptides. *Diabetes.* 1998;47(2):159-169.
24. Larsson H, Holst JJ, Ahren B. Glucagon-like peptide-1 reduces hepatic glucose production indirectly through insulin and glucagon in humans. *Acta Physiol Scand.* 1997;160(4):413-422.
25. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest.* 1998;101(3):515-520.
26. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2012;8(12):728-742.
27. Fonseca VA. New developments in diabetes management: medications of the 21st century. *Clin Ther.* 2014;36(4):477-484.
28. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet.* 2008;372(9645):1240-1250.
29. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet.* 2009;374(9683):39-47.

REFERENCES *(continued)*

30. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. *Ther Adv Endocrinol Metab.* 2015;6(1):19-28.
31. Bydureon [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals;2012.
32. Tanzeum [package insert]. Wilmington, DE: GlaxoSmithKline;2014.
33. Trulicity [package insert]. Indianapolis, IN: Eli Lilly and Company;2014.
34. Victoza [package insert]. Plainsboro, NJ: Novo Nordisk;2010.
35. Adlyxin [package insert]. Bridgewater, NJ: Sanofi-Aventis;2016.
36. Byetta [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals;2015.
37. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial. *Diabetes Care.* 2016;39(9):1501-1509.
38. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and Safety of Dulaglutide Versus Sitagliptin after 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5). *Diabetes Care.* 2014;37(8):2149-2158.
39. Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab.* 2006;8(4):436-447.
40. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care.* 2010;33(6):1389-1394.
41. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.
42. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
43. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015;373(23):2247-2257.
44. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* Published online: September 14, 2017 (doi: 10.1056/NEJMoa1612917).
45. Clinicaltrials.gov. Accessed September 21, 2017.
46. Rushforth B, McCrorie C, Glidewell L, Midgley E, Foy R. Barriers to effective management of type 2 diabetes in primary care: qualitative systematic review. *Br J Gen Pract*. 2016;66(643):e114-127.
47. Kruger DF, LaRue S, Estepa P. Recognition of and steps to mitigate anxiety and fear of pain in injectable diabetes treatment. *Diabetes Metab Syndr Obes.* 2015;8:49-56.
48. Holst JJ, Vilsboll T. Combining GLP-1 receptor agonists with insulin: therapeutic rationales and clinical findings. *Diabetes Obes Metab.* 2013;15(1):3-14.
49. Vora J, Bain SC, Damci T, et al. Incretin-based therapy in combination with basal insulin: a promising tactic for the treatment of type 2 diabetes. *Diabetes Metab.* 2013;39(1):6-15.
50. Buysman EK, Liu F, Hammer M, Langer J. Impact of medication adherence and persistence on clinical and economic outcomes in patients with type 2 diabetes treated with liraglutide: a retrospective cohort study. *Adv Ther.* 2015;32(4):341-355.
51. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab.* 2014;16(7):636-644.
52. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care.* 2014;37(10):2763-2773.
53. Rosenstock J, Hanefeld M, Shamanna P, et al. Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). *J Diabetes Complications.* 2014;28(3):386-392.
54. Pozzilli P, Norwood P, Jodar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes Obes Metab.* 2017;19(7):1024-1031.
55. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care.* 2014;37(8):2317-2325.
56. Soliqua [package insert]. Bridgewater, NJ: Sanofi-aventis;2016.
57. Xultophy [package insert]. Plainsboro, NJ: Novo Nordisk;2016.

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