There are 2 glucagon-like peptide-1 (GLP-1) receptor agonists currently approved by the US Food and Drug Administration for use in patients with type 2 diabetes mellitus (T2DM): exenatide and liraglutide.¹² These agents are important options in the treatment regimens for such patients. However, many patients express concerns about using these medications when recommended by physicians.

In the present article, we discuss several common questions asked by patients about GLP-1 receptor agonists. In the proposed answers, clinical decision points and the practical application of GLP-1 receptor agonists in the context of common patient concerns are illustrated.

**Case Presentation**

Susana is a 46-year-old woman who was diagnosed as having T2DM approximately 2 years ago. Initially, she adopted lifestyle modifications to manage her disease. Later, she began using metformin at a maximum dose of 2000 mg daily. With diet and exercise, she has been able to lose some weight. Currently, her body mass index is 35. Her glycosylated hemoglobin (HbA₁c) level continued to increase during the past year and is now 8.0%.

Susana’s health care provider recommends adding a GLP-1 receptor agonist to her treatment regimen, prompting her to ask several questions. The authors present these questions along with proposed answers, highlighting the practical application of GLP-1 receptor agonists in the context of common patient concerns.

**Why do I need to add a second agent? Why not just switch to a new one?**

Susana should be counseled about the beneficial effects of aggressive glycemic control.
control on microvascular complications, as demonstrated in numerous clinical trials. The benefits of glycemic control on macrovascular complications are less clear.4,5

Susana should also be educated about the importance of managing risk factors to decrease her risk of cardiovascular disease. Disease management should include education about the pathophysiologic progression of diabetes mellitus and appropriate therapeutic strategies, such as the use of combination therapies to attain glycemic targets.

When should I give myself the injection?
Glucagon-like peptide-1 receptor agonists should be initiated at the recommended initial dose and gradually increased to a maintenance dose. Exenatide is initiated at 5 μg twice daily for 30 days, followed by titration to 10 μg twice daily.1 Liraglutide is administered once daily without regard to proximity to meals, although patients should be encouraged to administer liraglutide at the same time each day.2 Liraglutide is usually initiated at 0.6 mg daily for 1 week, followed by titration to 1.2 mg daily for 1 to 2 weeks, then to 1.8 mg daily (if tolerated).2 In patients who experience problems related to liraglutide tolerability, it may be appropriate to remain at the lower dose.

I've read that a lot of patients experience nausea. How can I avoid this?
The most common adverse events reported with GLP-1 receptor agonists are gastrointestinal in nature, including nausea. Most episodes of nausea are of mild to moderate intensity, occurring more frequently at treatment initiation and abating over time. For example, in a 26-week head-to-head trial of exenatide and liraglutide, 12% to 18% of patients in both treatment groups experienced nausea within the first 6 weeks of the trial, and the incidence gradually decreased to approximately 10% and 3% for exenatide-treated and liraglutide-treated patients, respectively.6 Decreased persistence of nausea with liraglutide may be attributed to pharmacokinetic differences, compared with exenatide, or to improved patient adherence with the once-daily agent.

To maximize weight-loss benefits, the patient should take exenatide about 60 minutes before the meal because this timing produces maximum satiety. However, to reduce nausea, exenatide should be taken within the 30-minute period before the meal.

Susana should be counseled about potential nausea and fullness and advised to contact her health care provider in the event of severe or persistent nausea and vomiting. Eating slowly or consuming smaller meals may help reduce nausea. Studies have demonstrated the benefits of using prophylactic antiemetic agents to prevent nausea and vomiting, though these agents are associated with drowsiness and somnolence.7

Are these drugs safe?
Clinical trial results and spontaneous postmarketing reports of pancreatitis have prompted the addition of label warnings and precautions possibly associating this condition with GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.12 However, patients with T2DM frequently have risk factors for pancreatitis (eg, hypertriglyceridemia, obesity, advancing age) and receive medications associated with drug-induced pancreatitis, confounding assessment of the relationship between individual agents, T2DM, and the risk of pancreatitis. For example, analysis of a claims database indicated that patients with T2DM have a 2.8-fold greater risk of acute pancreatitis and a 1.9-fold greater risk of biliary disease compared with those of patients without diabetes mellitus.8

In addition, analysis of a large commercial health insurance database revealed no increased risk of acute pancreatitis associated with exenatide or sitagliptin compared with metformin or glyburide.9 Furthermore, review of preclinical and clinical data of the use of sitagliptin suggests no increased risk of pancreatitis in patients who were given that DPP-4 inhibitor.10

To our knowledge, neither GLP-1 receptor agonists nor DPP-4 inhibitors have been studied in patients with pancreatitis. Thus, these agents should not be used in individuals with pancreatitis or in those in whom a history of pancreatitis is suspected. Nonetheless, it is prudent to discuss current warnings about pancreatitis risks with patients to ensure an informed decision is made about initiating treatment. This counseling may also improve adherence to regimens, countering the influence of misinformation and nonmedical reports on patients’ decision making.

Patients who initiate use of a GLP-1 receptor agonist or a DPP-4 inhibitor should be questioned about pancreatitis during assessments of their medical histories. There is no evidence that baseline laboratory tests of lipase and amylase levels are necessary in patients who initiate incretin-related therapy. Other antidiabetic agents, such as oral medications or insulin, should be considered in patients at risk for pancreatitis, including patients with a history of pancreatitis.

Important Points About GLP-1 Receptor Agonists
These agents have beneficial effects on glycemic control.
These agents should be initiated at the recommended initial dose and gradually increased to a maintenance dose.
Most episodes of nausea associated with GLP-1 receptor agonists are of mild to moderate intensity, occurring more frequently at treatment initiation and abating over time. Eating slowly or consuming smaller meals may help reduce nausea.
There are warnings about possible pancreatitis risks associated with GLP-1 receptor agonists. These risks should be discussed thoroughly with patients.
Studies demonstrate similar lowering of glycosylated hemoglobin with GLP-1 receptor agonists compared with insulin. GLP-1 receptor agonists have additional benefits on body weight, and they help avoid hypoglycemia.

Figure. Important information about glucagon-like peptide-1 (GLP-1) receptor agonists for patients with diabetes mellitus.
history of alcohol abuse, or current gallstones. If pancreatitis is suspected, any GLP-1 receptor agonist or DPP-4 inhibitor should be discontinued, and these agents should not be restarted if pancreatitis is confirmed.

An increased incidence of thyroid C-cell tumors was observed with liraglutide administration in rodents, but not in humans. The liraglutide label includes a black box warning of thyroid C-cell cancer risk, noting that human relevance could not be determined by clinical or nonclinical studies. 

If I'll eventually need insulin, why not just start it now?

Susana's HbA1c level of 8% is lower than consensus recommendations for initiating insulin therapy. Although insulin is the most effective glucose-lowering agent, clinical trial data support the option of adding a GLP-1 receptor agonist rather than basal insulin early in therapy.

Susana should be informed about results of head-to-head comparisons of insulin glargine with exenatide or liraglutide. Such studies demonstrate similar HbA1c lowering with GLP-1 receptor agonists compared with insulin, and GLP-1 receptor agonists have additional beneficial effects on body weight.

Safety is another major point of consideration. Insulin therapy is highly effective, but it carries an approximately 10-fold increased risk of hypoglycemia. Therefore, if glucose level can be controlled, weight loss augmented, and hypoglycemia avoided, there is a strong argument for beginning a GLP-1 receptor agonist.

The availability of different but effective therapeutic options facilitates tailoring of treatment to meet the needs of the clinically heterogeneous population of individuals with T2DM. For Susana, the need to avoid additional weight gain depends strongly on the treatment option selected. Should a GLP-1 receptor agonist prove inadequate in achieving and maintaining her glucose target, there should be no hesitation about initiating an insulin therapy program.

References