

Practical Use of Glucagon-Like Peptide-1 Receptor Agonist Therapy in Primary Care

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Glucagon-like peptide-1 (GLP-1) receptor agonists are one of the newer classes of medications for the treatment of adults with type 2 diabetes. The GLP-1 receptor agonist class became available in 2005 in the United States with the approval of short-acting exenatide by the U.S. Food and Drug Administration (FDA). There are now three GLP-1 receptor agonists available: exenatide for twice-daily administration (BID), exenatide for once-weekly administration (QW), and liraglutide for once-daily administration. Other GLP-1 receptor agonists are in development.

The 2012 American Diabetes Association (ADA)/European Association for the Study of Diabetes position statement on a patient-centered approach to treating patients with type 2 diabetes¹ recommends GLP-1 receptor agonists as one of several choices for two- and three-drug combinations after initial treatment with lifestyle modification, exercise, diet, and metformin. GLP-1 receptor agonists are also recommended if metformin is contraindicated or not tolerated.

GLP-1 receptor agonists are one of five classes of medications recommended for two- and three-drug combinations (i.e., with a sulfonylurea [or meglitinide], thiazolidinedione, insulin, or dipeptidyl peptidase-4 [DPP-4] inhibitor), so selecting among the five classes can be challenging.¹ In addition to these five classes, other options include the

α -glucosidase inhibitors, bromocriptine, colesevelam, and pramlintide. This article reviews some of the benefits and limitations of the GLP-1 receptor agonist class, including differences within the class; describes how these agents allow for individualization of treatment; and offers some suggestions regarding practical considerations when using this class of medications.

Overview of Benefits and Limitations of GLP-1 Receptor Agonists

Pharmacological overview

The GLP-1 receptor agonist class has five important actions for patients with type 2 diabetes. The first is an increase in glucose-mediated insulin production by pancreatic β -cells.²⁻⁶ “Glucose-mediated” is an important nuance because insulin production and release remains under the control of the glucose-sensing mechanisms of β -cells and only occurs during hyperglycemia. As a consequence, there is a low incidence of hypoglycemia. In rat and mouse models, there is a

slowing of β -cell death.⁷⁻¹⁰ Conflicting data in humans involving a variety of measures of β -cell function make it unclear whether this is also a phenomenon in humans.¹¹⁻¹⁵ Other actions include a decrease or no change in fasting endogenous glucose release via a reduction in glycogenolysis but not gluconeogenesis and a reduction in glucagon secretion.^{3,16,17} The gastric emptying rate is also slowed, thereby slowing the absorption of carbohydrate, leading to a lower rise in plasma glucose.^{3,18} GLP-1 receptor agonists also act via the central nervous system, resulting in a sensation of satiety and reduced food intake.¹⁹⁻²¹ This effect explains, in part, the added benefit that many patients lose weight when taking a GLP-1 receptor agonist.^{11,15,22-26}

By comparison, DPP-4 inhibitors, which also act on the incretin system, do not slow the gastric emptying rate, promote satiety, reduce food intake, or promote weight loss.²⁷ These differences between DPP-4 inhibitors and GLP-1 receptor agonists are thought to result from differences in how the two classes exert their actions on the incretin system. DPP-4 inhibitors work indirectly by inhibiting the metabolism of native GLP-1 produced in the gut, thereby raising the level of endogenous GLP-1 to ~ 10 pmol/L.²⁸ By comparison, GLP-1 receptor agonists act directly on the GLP-1 receptor, providing a level of GLP-1 activity of ≈ 60 pmol/L of GLP-1.²⁹ From this, it is

IN BRIEF

The glucagon-like peptide-1 (GLP-1) receptor agonist class of medications has distinct benefits and limitations that provide an opportunity to individualize the treatment of patients with type 2 diabetes. Many strategies can be used to improve patient acceptance of and self-management with a GLP-1 receptor agonist.

Table 1. Head-to-Head Clinical Trials Comparing GLP-1 Receptor Agonists

	Exenatide BID	Exenatide QW	Liraglutide
Magnitude of lowering: ^{14,31–34}			
A1C (%)	0.8–1.5	1.3–1.9	1.1–1.5
FPG (mg/dl)	11–25	32–41	19–38
PPG (mg/dl)	124	95	Not rated
Gastric emptying rate	Slow	Slow	Little effect
Dosing frequency	Twice daily	Once weekly	Once daily
Dosing in relation to eating	Within 60 minutes of two major meals, at least 6 hours apart	Any time during the day regardless of meals	Any time during the day regardless of meals
Ease of administration	Prefilled pen; 29-, 30-, or 31-gauge needle	Kit that requires assembly; 23-gauge needle	Prefilled pen; 30- or 32-gauge needle
Onset of action	Days	Several weeks	Days

FBG, fasting blood glucose; PPG, postprandial glucose.

clear that DPP-4 inhibitors should not be considered an oral form of GLP-1 receptor agonist.

Benefits of GLP-1 receptor agonists

Beyond the low associated incidence of hypoglycemia and weight loss effects, GLP-1 receptor agonists offer several advantages that may be useful in individualizing therapy.

A1C reduction

A reduction in A1C of 0.5–1.5% has been reported with GLP-1 receptor agonists as monotherapy.^{11,15,22–24,30} Head-to-head clinical trials show significantly greater lowering of A1C with exenatide QW compared to exenatide BID,^{31,32} 1.8 mg liraglutide compared to exenatide BID,^{14,33} and 1.8 mg liraglutide compared to exenatide QW³⁴ (Table 1).

Effects on fasting and postprandial glucose

Although A1C reduction results from a lowering of both fasting blood glucose (FBG) and postprandial glucose (PPG), there are differences among the three GLP-1 receptor agonists. A 30-week comparison showed a

significantly greater reduction in FBG with exenatide QW compared to exenatide BID (reduction of 41 vs. 25 mg/dl, respectively, $P < 0.0001$). Both treatments resulted in significant improvements in seven-point self-monitoring of blood glucose (SMBG) profiles.³² Another investigation showed that exenatide BID resulted in a significantly greater reduction than liraglutide in PPG after breakfast and supper but not after lunch, whereas liraglutide resulted in a significantly greater reduction than exenatide BID in FBG.¹⁴ A 26-week comparison of exenatide QW and 1.8 mg liraglutide once daily showed reductions in A1C of 1.28 and 1.48% (95% CI 0.08–0.33), respectively.³⁵

Effects on cardiovascular biomarkers

Another benefit of GLP-1 receptor agonists is their impact on cardiovascular risk factors and biomarkers. GLP-1 receptor agonists cause a reduction of 1–7 mmHg in systolic blood pressure but have no significant effect on diastolic blood pressure.^{11,14,15,23,33,36–42} Improvements in lipid profile are also observed,

notably a reduction in triglycerides of 12–40 mg/dl.^{11,14,23,25,36,38–42} It is unclear whether these changes will have a beneficial outcome on cardiovascular event risk reduction. Long-term cardiovascular outcome trials are in progress with most GLP-1 receptor agonists.

Limitations of GLP-1 receptor agonists

As with all medications used to treat type 2 diabetes, GLP-1 receptor agonists have some limitations that should be discussed with patients when considering treatment options. Although hypoglycemia is common with many glucose-lowering agents, the occurrence of hypoglycemia with GLP-1 receptor agonists is generally low (Table 2). Focusing on the limitations that patients are more likely to experience (e.g., transient gastrointestinal [GI] adverse events) and how these limitations will be addressed is helpful in minimizing patients’ concerns. Providing patient education materials and involving other members of the diabetes health care team can further reassure patients that the limitations of GLP-1 receptor

Table 2. Hypoglycemia Rates in Head-to-Head Clinical Trials Comparing GLP-1 Receptor Agonists

	Exenatide BID Versus Liraglutide¹⁴ (n = 464)	Exenatide BID Versus Liraglutide³³ Extension (n = 389)	Exenatide BID Versus Exenatide QW³¹ (n = 252)	Exenatide BID Versus Exenatide QW³² (n = 295)	Exenatide QW Versus Liraglutide³⁴ (n = 911)
Hypoglycemia	Minor: 2.600 vs. 1.932 episodes/ patient-year Major: 2 vs. 0 episodes/ patient-year	Minor: 1.30 vs. 0.74 episodes/ patient-year	Minor: 3.3 vs. 3.9% Major: none	Minor: 5.4 vs. 6.1% Major: none	Minor: 15 vs. 12%* 4 vs. 3%** Major: none
*In those taking a concomitant sulfonylurea. **In those not taking a concomitant sulfonylurea.					

agonists will be addressed as needed to improve self-management.

Transient GI adverse events

Each of the GLP-1 receptor agonists, to varying degrees, can cause transient nausea and diarrhea. As monotherapy, nausea occurs in 8, 11, and 28% of patients treated with exenatide BID, exenatide QW, and liraglutide, respectively, whereas diarrhea is experienced by < 2, 11, and 17%, respectively.⁴³⁻⁴⁵ Similar GI adverse effects can occur with metformin; nausea/vomiting occurs in 26%, whereas diarrhea has been reported to lead to discontinuation in 6%.⁴⁶

GI adverse events are usually self-limiting. Nausea is usually mild and peaks within 8 weeks of starting exenatide BID and 4-8 weeks of starting liraglutide. Nausea resolves in all but ~ 10% within 28 weeks with exenatide BID and in 8 weeks with liraglutide.^{23,47,48} For exenatide QW, nausea peaks soon after initiation and resolves within 10 weeks in nearly all patients.¹⁵

These possible GI adverse events are important to discuss with patients because patients who are not expecting such situations may stop the medication believing that it

is a permanent problem. In addition, protracted vomiting, should it occur, may lead to pre-renal azotemia.

The most common approach to minimizing the risk and severity of nausea includes using a dose escalation strategy for exenatide BID and liraglutide; dose escalation is not needed for exenatide QW. Exenatide BID should be initiated at a dose of 5 µg twice daily and increased to 10 µg twice daily after 1 month based on clinical response. Exenatide BID should be taken within 60 minutes before the morning and evening meals. Liraglutide should be initiated at a dose of 0.6 mg once daily for 1 week and then increased to 1.2 mg once daily. If the 1.2-mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg once daily. One modification of this dose escalation strategy that is not described in the approved package inserts but that the author has found useful is to lengthen the time period during which dose escalation occurs.

Other strategies to help minimize the risk of nausea not described in the approved package insert include self-administering exenatide BID < 60 minutes before mealtime, temporarily

reducing the dose, or stopping eating when patients feel full.⁴⁹⁻⁵¹ Patients should be educated to avoid administering a GLP-1 receptor agonist close to a large or high-fat meal because doing so is likely to cause nausea. An advantage of exenatide QW and liraglutide is that they can be administered without regard to meal times.

Injection site reactions

Another possible limitation is the local irritation and nodule formation around the injection site that occurs most frequently with exenatide QW. The nodules, which are generally not visible but can be felt, typically last only a few weeks. Local irritation or nodule formation is usually a minor issue that can be prevented or managed by rotating injection sites in the abdomen, thigh, and upper arms.

Infrequent adverse events

As with other medications, infrequent adverse events are possible with glucose-lowering medications, including the GLP-1 receptor agonists. Although these adverse events may not be routinely discussed with patients, if questions arise, they should be discussed at a depth and in a manner appropriate for the patients based on their questions and previous

discussions and as part of a risk-benefit discussion. Patients should also be referred to the medication guide for each product for additional information.

Pancreatitis

One possible but infrequent adverse event is pancreatitis, which has been reported in post-marketing surveillance for all marketed GLP-1 receptor agonists and DPP-4 inhibitors. In clinical trials of liraglutide, 13 cases of pancreatitis (9 acute and 4 chronic) were reported in patients treated with liraglutide and 1 case was reported in a patient treated with glimepiride (2.7 vs. 0.5 cases/1,000 patient-years).⁴⁵

Analyses of two insurance claims databases show rates of pancreatitis that are similar among the glucose-lowering agents examined.^{52,53}

In one analysis ($n = 786,656$), the incidence rates (cases per 1,000 patient-years) were 5.7 for exenatide BID, 5.6 for sitagliptin, and 5.6 for metformin, sulfonylureas, or thiazolidinediones.⁵² Similar rates of acute pancreatitis over 1 year were observed in a second analysis among patients treated with exenatide BID, sitagliptin, metformin, or glyburide.⁵³

In contrast, an association between GLP-1 receptor agonist therapy and an increased risk of pancreatitis was found in two other analyses. In one, which examined the FDA database of reported adverse events from 2004 to 2009, the use of exenatide BID or sitagliptin increased the odds ratio for reported pancreatitis sixfold compared to other glucose-lowering agents.⁵⁴ In the other, Singh et al.⁵⁵ found an increased risk of acute pancreatitis with current or recent (within 2 years) use of a GLP-1 receptor agonist. These findings were based on the health records of 1,269 patients hospitalized with acute pancreatitis and matched controls.

The findings by Singh et al. were quickly challenged in a joint response from the ADA and the American Association of Clinical Endocrinologists (AACE),⁵⁶ which stated that this analysis “does not provide the basis for changing treatment in people with diabetes.” The joint statement by ADA and AACE noted that further clarity on this issue should come from nine prospective, controlled trials of GLP-1 receptor agonist therapy involving > 65,000 subjects. In the meantime, patients should be encouraged to speak to their providers to assess which treatments are best for them and to not stop therapy without consulting their provider.

The association of GLP-1 receptor agonists with pancreatitis is difficult to assess because of the nearly threefold greater risk of pancreatitis in people with type 2 diabetes compared to those without type 2 diabetes.⁵⁷ Until this issue is resolved, it is important to explain to patients the difference between the symptoms of pancreatitis and the minor, transient nausea described above. In addition, in patients with a history of pancreatitis, glucose-lowering agents other than exenatide BID⁴³ and exenatide QW⁴⁴ should be used, and liraglutide should be used with caution, according to the package inserts for each of these agents.⁴⁵

Potential risk of thyroid C-cell neoplasms

Although very rare in humans, another possible safety concern relates to the risk of thyroid C-cell neoplasms, which were found in preclinical studies with rats and mice but not with monkeys.^{58,59} Thyroid C-cell tumors were also observed in rodents not exposed to a GLP-1 receptor agonist, and expression of GLP-1 receptors in the thyroid C-cell tissues of humans and monkeys is low.⁵⁹

One of the conditions required by the FDA for making exenatide QW and liraglutide commercially available was to create a national registry of patients with thyroid tumors. The registry will allow monitoring to identify increases in the incidence of this problem in humans. If patients have a history of medullary C-cell tumors or multiple endocrine neoplasia-2 (thyroid, parathyroid, and pheochromocytoma tumors), they should not be treated with a GLP-1 receptor agonist.^{44,45}

Role of GLP-1 Receptor Agonists in Therapy

There are several clinical situations in which patients with type 2 diabetes may benefit from treatment with a GLP-1 receptor agonist. This includes patients who are taking metformin, a sulfonylurea, or a thiazolidinedione (alone or in combination) but are not at their glycemic goal, as well as patients with an A1C of 7–9%. However, for patients with an A1C > 9%, the addition of basal insulin should be strongly considered until glycemic control has improved. At that time, a decision can be made as to whether to continue basal insulin. Of the three GLP-1 receptor agonists, liraglutide and exenatide BID are indicated for use in combination with basal insulin.^{43,45}

Selection of a GLP-1 receptor agonist should be based on various clinical parameters. For example, if FBG is the primary target, exenatide QW or liraglutide are preferred over exenatide BID. Conversely, if PPG is the primary target, exenatide BID is preferred. Of course, other issues, including frequency of administration; side effects such as nausea, injection site reactions, and nodule formation; and patients' ability to use the administration devices are also important considerations.

It is important to realize that a small percentage of patients experi-

ence no or a minimal reduction in their blood glucose with a GLP-1 receptor agonist. Although the reason for this is unknown in most patients, in some it may be because they have been skipping doses or have reduced their dose. Because adverse events are a frequent reason for poor adherence, inquiring about medication difficulties such as adverse events at all follow-up visits can be helpful and provides an opportunity to find solutions that are acceptable to patients. It is most helpful to discuss with patients at the time of therapy initiation how to deal with common adverse events.

Other situations in which a GLP-1 receptor agonist might be a good choice include in older patients with type 2 diabetes, who are more likely to experience hypoglycemia unawareness.⁶⁰ In addition, limited data from clinical trials indicate that people ≥ 65 years of age experienced no difference in efficacy or safety compared to younger patients.^{43–45} However, assessment of renal function before initiation of a GLP-1 receptor agonist is suggested because older patients may experience a reduction in renal function.

Patients with renal impairment or end-stage renal disease (creatinine clearance < 30 ml/min) should not use exenatide BID or exenatide QW. Liraglutide can be used without dosage reduction but should be used with caution because data are limited regarding its use in patients with various stages of renal impairment.

Another group for whom a GLP-1 receptor agonist might be a good choice includes patients who experience excessive hunger or weight gain. It is not uncommon for patients to describe a sensation of “always being hungry.” GLP-1 receptor agonists have been noted clinically by some providers to blunt that sensation.

Finally, although the U.S. Federal Aviation Administration does not

allow insulin use for commercial pilots,⁶¹ and the U.S. Department of Transportation does not allow insulin use for commercial truck drivers,⁶² GLP-1 receptor agonists are allowed for pilots and are not mentioned in the list of medications of concern for commercial truck drivers.

Patients generally should not be placed on concurrent treatment with a GLP-1 receptor agonist and a DPP-4 inhibitor (i.e., alogliptin, linagliptin, saxagliptin, or sitagliptin). Although there are differences between the two classes of medications, both act on the incretin system. There is, however, preliminary evidence that the addition of exenatide BID to the combination of sitagliptin plus metformin produces additional (0.3%) A1C reduction beyond the combination of exenatide BID and metformin over 20 weeks.⁶³ Nonetheless, patients who are taking a DPP-4 inhibitor should discontinue it at the start of GLP-1 therapy.

Some additional patients also should not be considered for GLP-1 receptor agonist treatment. Such a therapy would not be appropriate in patients who have severe GI disease (e.g., gastroparesis).^{43,44} Patients who are pregnant or nursing should be excluded from using a GLP-1 receptor agonist, which are classified as pregnancy category C agents, unless the benefits outweigh the risks to the fetus.^{43–45} Because exenatide is cleared primarily by the kidneys, blood concentrations of exenatide (BID or QW) are not expected to be altered in patients with hepatic impairment.^{43,44} Liraglutide should be used cautiously, although no dose adjustment is recommended in patients with hepatic impairment.⁴⁵

Managing Expectations and Maximizing Acceptance of GLP-1 Receptor Agonist Therapy

Managing patient expectations from the outset is key to maximizing benefits and minimizing limitations associated with GLP-1 receptor agonist. One problem noted by the author with some frequency is that patients expect immediate results with this type of therapy. With exenatide BID and liraglutide, it is not uncommon to see glucose-lowering within the first few days. However, exenatide QW requires a few weeks to begin showing effects; maximal benefit may not be seen for up to 10 weeks.

In addition to patients' glycemic control expectations, it is especially important to manage their expectations with regard to weight. It is not uncommon for patients to ask about “those new medications that cause weight loss.” GLP-1 receptor agonists should not be presented to patients as weight loss drugs. It must be made clear that, although weight loss occurs in $\sim 80\%$ of patients,⁶⁴ it is not possible to identify which patients will lose weight before initiating the therapy.

In the author's experience, patients fit into one of three groups with respect to the weight effects of the GLP-1 receptor agonists. The first is the small percentage of patients who do not lose weight but have the expected 0.5–1.5% reduction in A1C. For these patients, the lack of a weight effect should not be viewed as a clinical failure. The second group is those who experience a 2- to 5-lb weight loss, and the third group includes those who have a greater weight loss, perhaps as much as 20–40 lb. Some patients in the third group subsequently regain some of their lost weight.

Although patients with a BMI > 30 or 35 kg/m² are generally those who experience the greatest weight loss,⁶⁵ this has not always been the

case in the author's experience, in which some patients with a BMI < 30 kg/m² have been observed to lose 15–20 lb. The loss in weight usually plateaus in about 8 weeks with exenatide BID and 8–12 weeks with liraglutide.

Consideration of a GLP-1 receptor agonist should involve discussing with patients their comfort with delivering a medication subcutaneously. This can be a significant issue for patients and providers, with concerns similar to those that arise when considering starting insulin.⁶⁶ Patient concerns include having to use a needle and give a “shot,” the social stigma associated with using an injected medication, the perceived complexity of the delivery system, and the belief that this in some way signifies that the disease process is getting worse. Providers also have concerns, including feeling that it takes more time to educate patients about using a subcutaneous medication, the availability and qualification of staff to teach patients how to use these medications, and concerns that patients will not accept their recommendation to use a GLP-1 receptor agonist. Such concerns on the part of patients and providers can create an environment of reluctance to advance diabetes care, thereby making it difficult for patients to attain glycemic control.⁶⁷

Addressing patient barriers

Numerous strategies can be implemented to address potential patient barriers. First, it may be helpful to ask patients if they have any concerns or issues they would like to discuss. Many patients with type 2 diabetes have searched for information online, talked with neighbors, or have otherwise gained some secondhand knowledge about these medications.

Once patients' concerns are identified, it is much easier to address them. It may not be pos-

sible to address more than two or three issues during a clinic visit, but patients should be assured that remaining issues will be addressed in subsequent visits or, alternatively, by other members of the diabetes health care team.

It is also important to avoid suggesting that advancing to this (or any other) glucose-lowering medication signifies that the disease is getting worse. Rather it is important to make clear that diabetes is a progressive illness that requires medication adjustment to maintain management goals.

Clinicians may find it especially helpful to discuss with patients the benefits and limitations of GLP-1 receptor agonists, noting that they are much less likely than insulin therapy to cause hypoglycemia or weight gain. The potential of losing weight with a GLP-1 receptor agonist can be a strong motivator for patients who have struggled with weight gain while using other glucose-lowering agents. Similarly, learning that the risk of hypoglycemia is much lower than with insulin or a secretagogue may help relieve patients' anxiety. It can also be valuable to have patients check their FBG and PPG levels a few times for the week or two after starting GLP-1 receptor agonist therapy. Seeing these levels decrease can be another motivating factor that can blunt initial concerns regarding issues such as self-injection and GI adverse effects.

Two of the GLP-1 receptor agonists, liraglutide and exenatide QW, do not require dose timing with meals. Remembering to take a medication in advance of a meal, as is necessary for exenatide BID, can be challenging for some patients.

All three of the GLP-1 receptor agonists have administration devices/systems that make both the dosing and teaching of the medica-

tions relatively simple. Liraglutide and exenatide BID are delivered with pen devices with 31- or 32-gauge needles, whereas exenatide QW has a delivery kit that simplifies the mixing of diluent and powdered medication but requires a syringe with an 8-mm, 23-gauge needle. Despite the larger-gauge administration needle required with exenatide QW, some patients may decide that the once-weekly administration is a key benefit because they can select the day of the week that they want to administer their dose and stick with it. Other patients may decide they like the once-daily administration of liraglutide because they do not need to worry about timing their dose with a meal.

Because patients usually have concerns about giving themselves an injection, avoiding use of the word “shot” is suggested. Patients associate shots with painful antibiotic and vaccine injections they have had in the past. It is also helpful to acknowledge that not wanting to “stick holes” in themselves is a very rational decision. Differentiating subcutaneous administration from intramuscular injection is important. GLP-1 receptor agonists use much smaller, shorter needles and are delivered into the subcutaneous fat. They are not intramuscular injections.

It is often helpful to patients to make a connection between doing something that they perceived as unpleasant and attaining the goals that they want to attain. Although it is important to establish and follow achievement of the numeric goals of diabetes control, it is also important to emphasize the greater sense of well-being patients may feel when they achieve improved blood glucose control.

Addressing these issues and educating people with type 2 diabetes is a team process. The author

typically discusses treatment options with patients, explaining the benefits and limitations of each choice. Once a decision is made, much of the detailed patient education is provided by clinic staff. For this reason, it is important to work with staff to develop a coordinated process that can be followed when patients begin therapy with a GLP-1 receptor agonist or other glucose-lowering therapy. It is important that the teaching is consistent from both providers and support staff

when providing patient education. In addition, it is important for those involved in providing patient education to be knowledgeable about the disease and the treatments, including how each delivery device works. For the three GLP-1 receptor agonists, understanding—and demonstrating—the differences among the devices is crucial before presenting to patients.

Local diabetes education programs and certified diabetes educators can be quite helpful

with this process. More information about how to find a local diabetes educator may be found at the American Association of Diabetes Educators website (<http://www.diabeteseducator.org/DiabetesEducation/Find.html>). In addition, a wide variety of patient education resources are available from the ADA (<http://www.diabetes.org/living-with-diabetes/?loc=GlobalNavLWD>) and AACE (<http://resources.aace.com>).

Table 3. Strategies to Improve Patient Acceptance and Self-Management With a GLP-1 Receptor Agonist

Manage patient expectations before initiating GLP-1 receptor agonist therapy.

- Avoid presenting GLP-1 receptor agonists as weight loss medications.

Investigate concerns (e.g., needle phobia, cost, and perceived complexity) before initiating therapy.

To allay concerns for patients with needle phobia:

- Familiarize patients (and yourself) with pen devices or delivery kit.
- Avoid use of the word “shot.”
- Differentiate between subcutaneous and intramuscular injections.
- Have patients self-inject the first dose in the office; alternatively, just use the needle.

To enhance patient motivation for initiating GLP-1 receptor agonist therapy:

- Help patients make the connection between doing something that is perceived as unpleasant and the goals they want to attain, including a greater sense of well-being.
- Discuss benefits such as weight loss and the low incidence of hypoglycemia.
- Encourage patients to perform SMBG a few times daily for a week or two after initiating to see reductions in FBG and PPG levels.
- Involve a dietitian to help patients identify strategies to maximize the potential for weight loss.
- Explain that GLP-1 receptor agonists help patients lose weight by promoting satiety, leading to decreased caloric intake, and not by altering metabolism.
- Advise patients to eat meals without distractions such as television.
- Advise patients to eat a small portion and then wait 30 minutes before eating more, to allow satiety to occur.
- Counsel patients to stop eating when they feel full.

To address nausea:

- Before initiation, educate patients that transient nausea is possible.
- Use a dose escalation strategy for exenatide BID or liraglutide, but not for exenatide QW, as described in package inserts.
 - Consider lengthening the time over which the dose is escalated.
- Administer exenatide BID < 60 minutes before the meal.
- Temporarily reduce the dose.
- Counsel patients to stop eating when they feel full.
- Avoid administering the medication close to a large or high-fat meal.

Educate patients regarding the possibility of localized irritation or nodule formation at injection site. Advise rotating injection among sites in the abdomen, thigh, and upper arms.

Assess adherence if the glycemic response is less than expected (e.g., A1C reduction < 0.5%).

Summary

The GLP-1 receptor agonist class of medications offers health care providers an important novel treatment option with distinct benefits and limitations compared to other classes of glucose-lowering medications. Working in collaboration with patients, providers and their staff can individualize treatment and implement strategies to improve patient acceptance and self-management with a GLP-1 receptor agonist (Table 3). Doing so will undoubtedly help patients with type 2 diabetes attain their metabolic and treatment goals.

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REFERENCES

- ¹Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR: Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35:1364–1379, 2012
- ²Drucker DJ: The biology of incretin hormones. *Cell Metab* 3:153–165, 2006
- ³Naslund E, Bogefors J, Skogar S, Gryback P, Jacobsson H, Holst JJ, Hellstrom PM: GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol* 277:R910–R916, 1999
- ⁴Fehmman HC, Habener JF: Insulinotropic hormone glucagon-like peptide-I(7-37) stimulation of proinsulin gene expression and proinsulin biosynthesis in insulinoma beta TC-1 cells. *Endocrinology* 130:159–166, 1992
- ⁵Kreymann B, Williams G, Gbatei MA, Bloom SR: Glucagon-like peptide-1 7-36: a physiological incretin in man. *Lancet* 2:1300–1304, 1987
- ⁶Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, Hufner M, Schmiegel WH: Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab* 87:1239–1246, 2002
- ⁷Bulotta A, Hui H, Anastasi E, Bertolotto C, Boros LG, Di MU, Perfetti R: Cultured pancreatic ductal cells undergo cell cycle redistribution and beta-cell-like differentiation in response to glucagon-like peptide-1. *J Mol Endocrinol* 29:347–360, 2002
- ⁸Farilla L, Bulotta A, Hirshberg B, Li CS, Khoury N, Noshmehr H, Bertolotto C, Di MU, Harlan DM, Perfetti R: Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology* 144:5149–5158, 2003
- ⁹Xu G, Stoffers DA, Habener JF, Bonner-Weir S: Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. *Diabetes* 48:2270–2276, 1999
- ¹⁰Zhou J, Wang X, Pineyro MA, Egan JM: Glucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon- and insulin-producing cells. *Diabetes* 48:2358–2366, 1999
- ¹¹Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, Brodows RG: Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 30:1448–1460, 2008
- ¹²Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Jarvinen H, Heine RJ: One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 32:762–768, 2009
- ¹³Mari A, Degn K, Brock B, Rungby J, Ferrannini E, Schmitz O: Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on beta-cell function in normal living conditions. *Diabetes Care* 30:2032–2033, 2007
- ¹⁴Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L: 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* 374:39–47, 2009
- ¹⁵Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzalez JG, Chan M, Wolka AM, Boardman MK: Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care* 35:252–258, 2012
- ¹⁶Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, Schmitz O: One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53:1187–1194, 2004
- ¹⁷Seghieri M, Rebelos E, Gastaldello A, Astiarraga BD, Casolaro A, Barsotti E, Poci A, Nauck M, Muscelli E, Ferrannini E: Direct effect of GLP-1 infusion on endogenous glucose production in humans. *Diabetologia* 56:156–161, 2013
- ¹⁸Delgado-Aros S, Kim DY, Burton DD, Thomforde GM, Stephens D, Brinkmann BH, Vella A, Camilleri M: Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. *Am J Physiol Gastrointest Liver Physiol* 282:G424–G431, 2002
- ¹⁹Gutzwiller JP, Goke B, Drewe J, Hildebrand P, Ketterer S, Handschin D, Winterhalder R, Conen D, Beglinger C: Glucagon-like peptide-1: a potent regulator of food intake in humans. *Gut* 44:81–86, 1999
- ²⁰Gutzwiller JP, Drewe J, Goke B, Schmidt H, Rohrer B, Lareida J, Beglinger C: Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am J Physiol* 276:R1541–R1544, 1999
- ²¹DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L: Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin* 24:2943–2952, 2008
- ²²Nelson P, Poon T, Guan X, Schnabel C, Wintle M, Fineman M: The incretin mimetic exenatide as a monotherapy in patients with type 2 diabetes. *Diabetes Technol Ther* 9:317–326, 2007
- ²³Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B: Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 373:473–481, 2009
- ²⁴Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B: Liraglutide, a once-daily human glucagon-like peptide-1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab* 13:348–356, 2011
- ²⁵Taylor K, Gurney K, Han J, Pencek R, Walsh B, Trautmann M: Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years. *BMC Endocr Disord* 11:9, 2011
- ²⁶Nauck M, Frid A, Hermansen K, Thomsen AB, Daring M, Shah N, Tankova T, Mitha I, Matthews DR: Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year

results from the LEAD-2 study. *Diabetes Obes Metab* 15:204–212, 2013

²⁷Morales J: The pharmacologic basis for clinical differences among GLP-1 receptor agonists and DPP-4 inhibitors. *Postgrad Med* 123:189–201, 2011

²⁸Herman GA, Bergman A, Stevens C, Kotey P, Yi B, Zhao P, Dietrich B, Golor G, Schrodter A, Keymeulen B, Lasseter KC, Kipnes MS, Snyder K, Hilliard D, Tanen M, Cilissen C, De Smet M, de Lepeleire I, Van Dyck K, Wang AQ, Zeng W, Davies MJ, Tanaka W, Holst JJ, Deacon CF, Gottesdiener KM, Wagner JA: Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *J Clin Endocrinol Metab* 91:4612–4619, 2006

²⁹Holst JJ, Deacon CF: Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. *Diabetologia* 48:612–615, 2005

³⁰Vilsboll T, Zdravkovic M, Le Thi T, Krarup T, Schmitz O, Courreges JP, Verhoeven R, Buganova I, Madsbad S: Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 30:1608–1610, 2007

³¹Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, Trautmann M, Porter L: DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96:1301–1310, 2011

³²Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, Porter L: Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 372:1240–1250, 2008

³³Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, Blonde L, Rosenstock J: Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care* 33:1300–1303, 2010

³⁴Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, Hoogwerf BJ, Gao A, Boardman MK, Fineman M, Porter L, Scherthaner G: Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 381:117–124, 2013

³⁵Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, Hoogwerf BJ, Gao A, Boardman MK, Fineman M, Porter L, Scherthaner G: Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 381:117–124, 2013

³⁶Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Sondergaard RE, Davies M: Liraglutide versus sitagliptin for patients with type 2

diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 375:1447–1456, 2010

³⁷Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, Wilhelm K, Malone J, Porter LE: Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 376:431–439, 2010

³⁸Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, Taylor KL, Trautmann ME, Kim DD, Kendall DM: 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* 8:436–447, 2006

³⁹Zinman B, Hoogwerf BJ, Garcia SD, Milton DR, Giaconia JM, Kim DD, Trautmann ME, Brodows RG: The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 146:477–485, 2007

⁴⁰Russell-Jones D, Vaag A, Schmitz O, et al.: Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 52:2046–2055, 2009

⁴¹Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, Hale PM, Zdravkovic M, Blonde L: Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 32:1224–1230, 2009

⁴²Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, Brodows R, Trautmann M: A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 50:259–267, 2007

⁴³Byetta package insert. San Diego, Calif., Amylin Pharmaceuticals, 2011

⁴⁴Bydureon package insert. San Diego, Calif., Amylin Pharmaceuticals, 2012

⁴⁵Victoza package insert. Princeton, N.J., Novo Nordisk, 2012

⁴⁶Glucophage package insert. Princeton, N.J., Bristol-Myers Squibb, 2011

⁴⁷DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092–1100, 2005

⁴⁸Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, During M, Matthews DR: Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide

effect and action in diabetes)-2 study. *Diabetes Care* 32:84–90, 2009

⁴⁹Cobble ME: How to implement incretin therapy. *J Fam Pract* 57:S26–S31, 2008

⁵⁰Freeman JS: Optimizing outcomes for GLP-1 agonists. *J Am Osteopath Assoc* 111:eS15–eS20, 2011

⁵¹Unger JR, Parkin CG: Glucagon-like peptide-1 (GLP-1) receptor agonists: differentiating the new medications. *Diabetes Ther* 2:29–39, 2011

⁵²Garg R, Chen W, Pendergrass M: Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 33:2349–2354, 2010

⁵³Dore DD, Seeger JD, Arnold CK: Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin* 25:1019–1027, 2009

⁵⁴Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC: Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 141:150–156, 2011

⁵⁵Singh S, Chang HY, Richards TM, Weiner JP, Clarke JM, Segal JB: Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med*. Electronically published in 2013 (doi:10.1001/jamainternmed.2013.2720)

⁵⁶American Association of Clinical Endocrinologists, American Diabetes Association issue joint response to published *JAMA* article [article online]. Available from <http://media.aace.com/press-release/correcting-and-replacing-american-association-clinical-endocrinologists-american-diabe>. Accessed 16 August 2013

⁵⁷Noel RA, Braun DK, Patterson RE, Bloomgren GL: Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 32:834–838, 2009

⁵⁸Parks M, Rosebraugh C: Weighing risks and benefits of liraglutide: the FDA's review of a new antidiabetic therapy. *N Engl J Med* 362:774–777, 2010

⁵⁹Knudsen LB, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, Gotfredsen C, Egerod FL, Hegelund AC, Jacobsen H, Jacobsen SD, Moses AC, Molck AM, Nielsen HS, Nowak J, Solberg H, Thi TD, Zdravkovic M: Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 151:1473–1486, 2010

⁶⁰Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B: Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. *Diabetes Care* 32:1513–1517, 2009

⁶¹Guide for aviation medical examiners. Pharmaceuticals (Therapeutic medications) [article online]. Available from <http://www>.

faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/pharm. Accessed 16 August 2013

⁶²Medical examination report for commercial driver fitness determination [article online]. Available from <http://www.fmcsa.dot.gov/documents/safetyprograms/medical-report.pdf>. Accessed 16 August 2013

⁶³Violante R, Oliveira JH, Yoon KH, Reed VA, Yu MB, Bachmann OP, Ludemann J, Chan JY: A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin. *Diabet Med* 29:e417–e424, 2012

⁶⁴Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, Wintle ME, Maggs DG: Exenatide effects

on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin* 24:275–286, 2008

⁶⁵Niswender K, Pi-Sunyer X, Buse J, Jensen KH, Toft AD, Russell-Jones D, Zinman B: Weight change with liraglutide and comparator therapies: an analysis of seven phase 3 trials from the liraglutide diabetes development programme. *Diabetes Obes Metab* 15:42–54, 2013

⁶⁶Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV: Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. *Diabetes Care* 28:2543–2545

⁶⁷Koerbel G, Korytkowski M: Insulin-therapy resistance: another form of

insulin resistance in type 2 diabetes. *Practical Diabetology* 22:36–40, 2003

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