Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes

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ABSTRACT

The incretin system has become an important target in the treatment of type 2 diabetes in recent years, and glucagon-like peptide 1 (GLP-1) is of particular interest for its glucose-lowering effects. The physiological response to oral ingestion of nutrients, involving the incretin system, is reduced in some patients with type 2 diabetes but may be augmented by administration of GLP-1 receptor agonists. The GLP-1 receptor agonists currently approved in the United States for the treatment of type 2 diabetes include exenatide (administered twice daily), liraglutide and lixisenatide (administered once daily), and the once-weekly agents exenatide extended-release, albiglutide, and dulaglutide. These agents have been shown to reduce A1C (by ~0.8–1.6%), body weight (by ~1–3 kg), blood pressure, and lipids. GLP-1 receptor agonists are associated with a low risk of hypoglycemia, and the most common adverse effects are gastrointestinal. Proper patient selection and education can assist in achieving positive treatment outcomes.

The incretin system has become an important target in the treatment of type 2 diabetes in recent years (1). Incretins are hormones produced by the intestinal mucosa in response to oral intake of nutrients that enhance glucose-stimulated insulin secretion and lower blood glucose levels. Incretins also reduce insulin release when glucose levels are near normal. It has been shown that secretion of insulin is greater in response to oral glucose ingestion than to an isoglycemic intravenous glucose infusion, a phenomenon referred to as "the incretin effect" (2,3). Two incretin hormones have been identified: glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 (GLP-1) (4). GLP-1 is of particular interest for its glucose-lowering effects (5), as well as its ability to slow gastric emptying and suppress secretion of glucagon (1).

The incretin effect is reduced in people with type 2 diabetes (6). The most recent understanding of this deficit suggests that it relates to deterioration of the GLP-1 effect, with impaired capacity to secrete insulin, increasing insulin resistance, and hyperglycemia, perhaps leading to a decrease in GLP-1 receptor expression and resulting in GLP-1 resistance (7). Administration of GLP-1 receptor agonists stimulates GLP-1 receptors, thereby increasing insulin secretion in response to oral and intravenous glucose to similar extents; this means the magnitude of the incretin effect should remain unchanged (8). Several GLP-1 receptor agonists are now approved in the United States for the treatment of type 2 diabetes. The purpose of this article is to review the mechanism of action of GLP-1 receptor agonists in type 2 diabetes and discuss the available treatment

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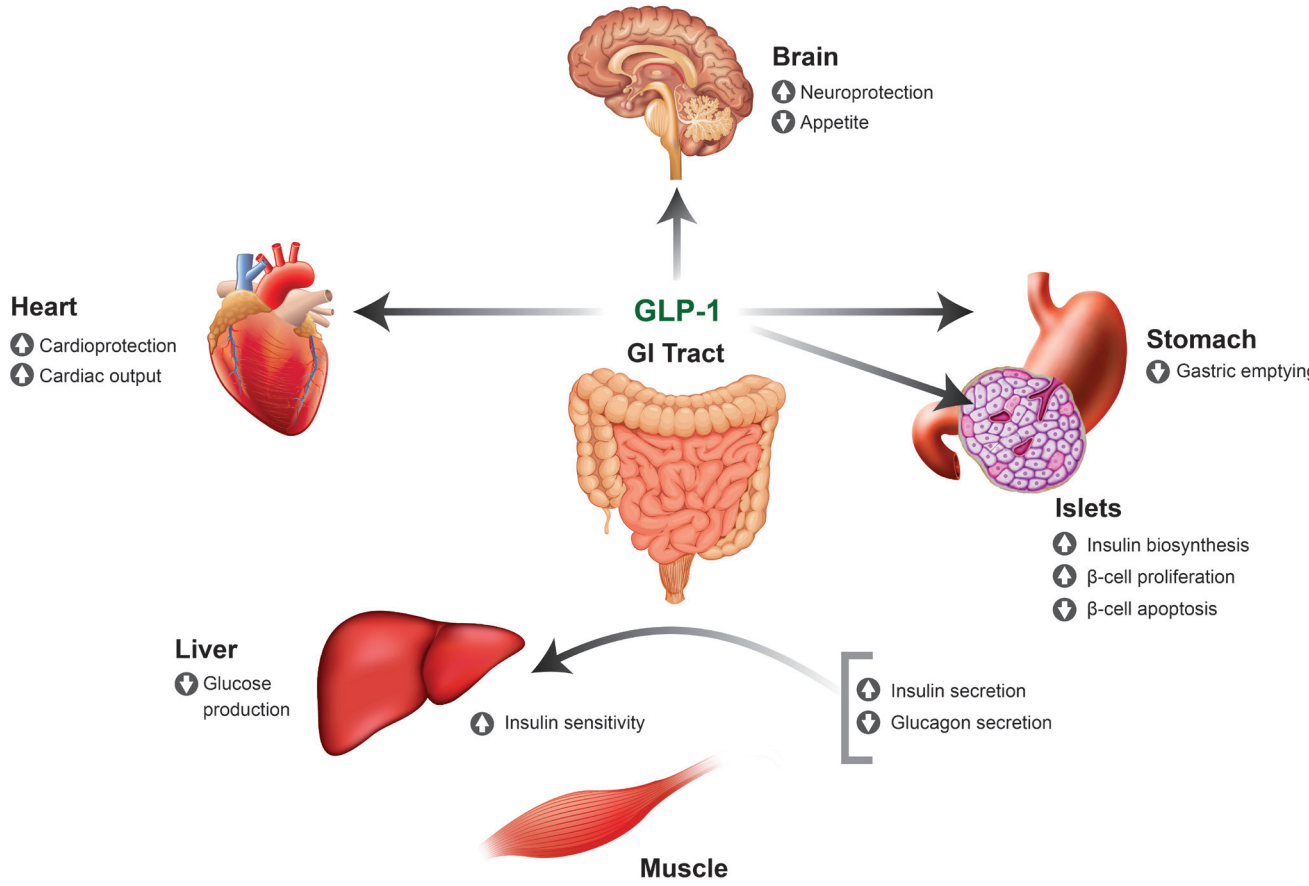

FIGURE 1. Actions of GLP-1 in target tissues. Adapted with permission from ref. 9. GI, gastrointestinal.

options in this drug class, including key clinical benefits, safety considerations, and practical information about patient selection, education, prescribing, and safety monitoring.

Pharmacological Effects of GLP-1

GLP-1 has a number of potentially beneficial effects in the setting of type 2 diabetes (Figure 1) (9). Intravenous administration of exogenous GLP-1 to patients with type 2 diabetes was shown to reduce plasma glucose concentrations to the normal fasting range, even in patients who had an inadequate response to oral antihyperglycemic drugs (10). The effects of exogenous GLP-1 observed after administration to patients with type 2 diabetes (11) include:

- Decreased glucagon concentrations
- Improved insulin sensitivity
- Decreased A1C
- Slowed gastric emptying
- Increased satiety
- Decreased free fatty acid concentrations
- Decreased body weight

However, the therapeutic use of native GLP-1 is limited by its very short half-life and rapid degradation. The development of GLP-1 receptor agonists that are resistant to degradation overcame this limitation (12).

Overview of Available GLP-1 Receptor Agonists

A number of GLP-1 receptor agonists have become available in the United States since the approval of the first agent in the class, exenatide, more than 10 years ago. These include the short-acting agents exenatide twice daily (BID) (13), intermediate-acting liraglutide (administered once daily) (14), and the long-acting agents administered once weekly (QW), including exenatide QW (15), albiglutide (16), and dulaglutide (17). Lixisenatide (administered once daily) has also recently been approved in the United States (18). Properties of these agents are summarized in Table 1.

With exenatide BID, peak plasma exenatide concentrations are reached 2.1 hours after administration, and the terminal half-life is 2.4 hours (13). Exenatide BID should be administered within 60 minutes before the two main meals of the day. Lixisenatide is administered once daily 1 hour before the first meal of the day. Its half-life is ~3 hours (18). The half-life of liraglutide is 12.6 hours (19), and it is administered once daily at any time without regard to meals (14). The extended-release formulation of exenatide contains the same active compound as in exenatide BID, encapsulated in microspheres that slowly degrade and provide continuous release of

TABLE 1. Overview of GLP-1 Receptor Agonists Available in the United States for the Treatment of Type 2 Diabetes

Generic (Trade) Name; Manufacturer	Dosing Frequency	Recommended Dosage	Administration Before Meals Required?	Available Dosage Form(s); Needle Requirements
Short-acting				
Exenatide BID (Byetta); AstraZeneca (13)	Twice daily	5 µg subcutaneously twice daily within 60 minutes before meals; after 1 month, may increase to 10 µg subcutaneously twice daily based on clinical response	Yes	5-µg pen, 250 µg/mL (1.2 mL); 29-, 30-, or 31-gauge pen needles
Lixisenatide (Adlyxin); Sanofi (18)	Once daily	10 µg subcutaneously once daily within 1 hour before the first meal of the day; on day 15, increase to 20 µg once daily	Yes	50 µg/mL in 3-mL green prefilled pen (14 10-µg doses); 100 µg/mL in 3-mL burgundy pre-filled pen (14 20-µg doses)
Intermediate-acting				
Liraglutide (Victoza); Novo Nordisk (14)	Once daily	0.6 mg subcutaneously once daily for 1 week, then increase to 1.2 mg once daily; if glycemic control not acceptable, can increase dose to 1.8 mg subcutaneously once daily	No	Multi-dose pen delivers 0.6, 1.2, or 1.8 mg, 6 mg/mL (3 mL); 32-gauge pen needles
Long-acting				
Exenatide QW (Bydureon); AstraZeneca (15)	Once weekly	2 mg subcutaneously once weekly (every 7 days) with or without meals	No	Single-dose 2-mg vial and 2-mg pen (require reconstitution); 23-gauge 7-mm needles supplied with pen
Albiglutide (Tanzeum); GlaxoSmithKline (16)	Once weekly	30 mg subcutaneously once weekly; may increase to 50 mg subcutaneously once weekly for inadequate glycemic control	No	Single-dose 30- and 50-mg pens (require reconstitution for 15 [30 mg] to 30 [50 mg] minutes after mixing); 29-gauge, 5-mm, thin-wall needle supplied with pen
Dulaglutide (Trulicity); Eli Lilly (17)	Once weekly	0.75 mg subcutaneously once weekly; may increase to 1.5 mg subcutaneously once weekly for inadequate glycemic control	No	Single-dose pen or prefilled syringes: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL; 29-gauge needle attached to pen

the drug (20). Albiglutide and dulaglutide, the other long-acting GLP-1 receptor agonists, each have a half-life of ~5 days (16,17).

Clinical Effects of GLP-1 Receptor Agonists in Type 2 Diabetes

Effects on Glycemic Control

Glycemic control is the primary goal of antihyperglycemic therapy. Results of a meta-analysis of clinical studies (21) indicate that treatment with GLP-1 receptor agonists is associated with A1C reductions from baseline of −0.42% for exenatide 5 µg BID, −0.50% for lixisenatide 20 µg once daily, −0.69% for albiglutide 30 mg QW, −0.71% for liraglutide 1.2 mg once daily, −0.75% for exenatide 10 µg BID, −1.03% for liraglutide 1.8 mg once daily, and −1.09% for exenatide 2 mg QW and dulaglutide 1.5 mg QW versus placebo. The mean changes in A1C reported in clinical studies of 24–52 weeks' duration in the drugs' prescribing information (13–17) are shown in Figure 2. In studies of GLP-1 receptor agonists used alone or in combination with oral antihyperglycemic therapies, mean changes in A1C ranged from −0.8 to −1.7% for exenatide BID, −0.8 to −1.5% for liraglutide 1.2–1.8 mg once daily, −0.6 to −0.9% for lixisenatide once daily, −0.6 to −0.9% for albiglutide 30–50 mg QW, −0.7 to −1.6% for dulaglutide 0.75–1.5

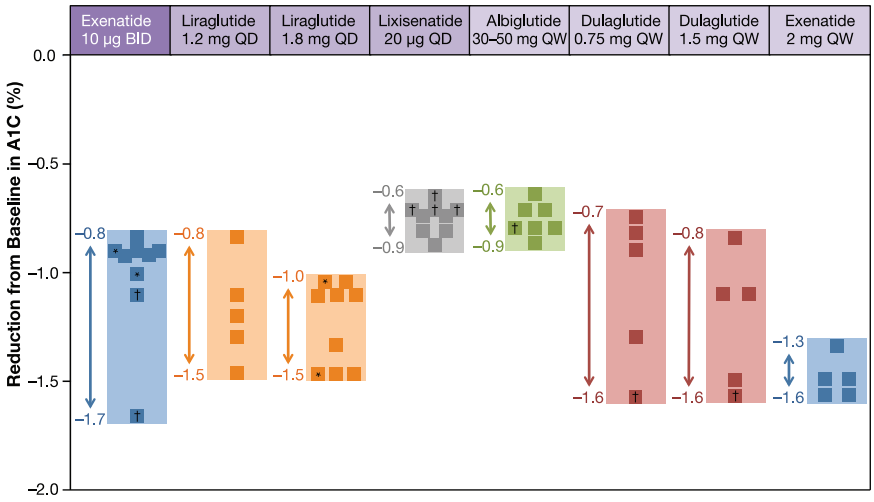

FIGURE 2. Range of mean changes from baseline in A1C in clinical studies of 24–52 weeks' duration reported in prescribing information for five GLP-1 receptor agonists (13–18). Each square represents the finding from one study. Drugs were tested as monotherapy or in combination with oral medications except as noted. *Finding reported as comparator in clinical study in another drug's prescribing information. †Finding for drug in combination with insulin. QD, once daily.

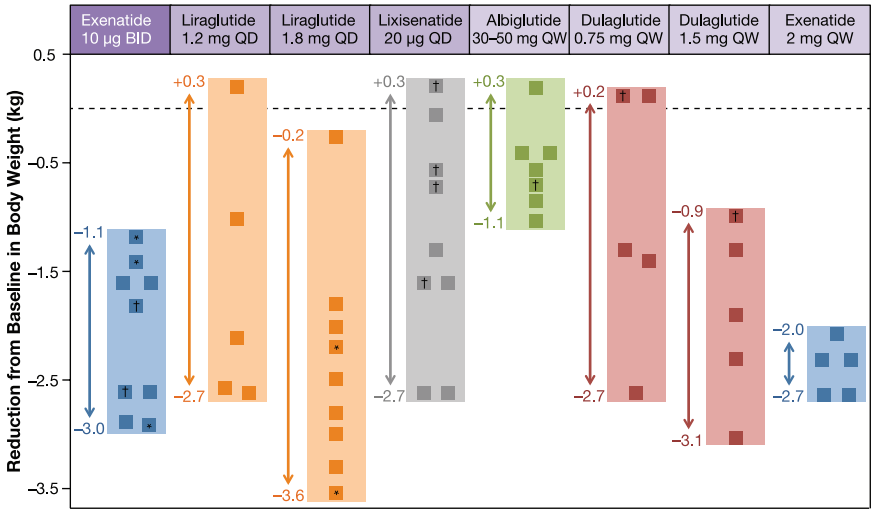

FIGURE 3. Range of mean changes from baseline in body weight in clinical studies of 24–52 weeks' duration reported in prescribing information for five GLP-1 receptor agonists (13–18). Each square represents findings from one study. Drugs were tested as monotherapy or in combination with oral medications except as noted. *Finding reported as comparator in clinical study in another drug's prescribing information. †Finding for drug in combination with insulin. QD, once daily.

mg QW, and −1.3 to −1.6% for exenatide QW (13–18).

Effects on Body Weight

A recent update to the American Heart Association/American Diabetes Association (AHA/ADA) guidelines on cardiovascular disease (CVD) prevention in adults with type 2 diabetes highlights weight management as a key component and suggests that health care providers consider using antihyperglycemic drugs that produce weight loss, including the GLP-1 receptor agonists (22). The 2015 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) clinical practice guidelines also note the importance of weight management in patients with type 2 diabetes and recommend the use of antihyperglycemic agents that are associated with weight loss or at least have a neutral effect on body weight (23).

Body weight reduction was a common effect observed in clinical trials evaluating GLP-1 receptor agonists in patients with type 2 diabetes. In a mixed-treatment comparison meta-analysis of randomized controlled trials of GLP-1 receptor agonists (exenatide BID and QW and liraglutide) in overweight or obese patients with type 2 diabetes, mean reductions in body weight were greater than with placebo for exenatide 10 µg BID (–1.4 kg), exenatide QW (–1.6 kg), and liraglutide 1.8 mg (–1.5 kg), with no significant differences among these three treatments (24). Changes in body weight reported in clinical studies in the drugs' prescribing information (13–18) are shown in Figure 3. In clinical trials of once-daily or BID GLP-1 receptor agonists (liraglutide, lixisenatide, or exenatide BID), mean changes in body weight were −2.1 to −2.9 kg for monotherapy and +0.3 to −3.6 kg in combination with oral antihyperglycemic therapies (13,14,18). In trials of weekly GLP-1 receptor agonists (exenatide QW, albiglutide, or dulaglutide), mean changes in body weight were −0.7 to −1.6 kg for monotherapy and +0.3 to −3.1 kg in combination with oral antihyperglycemic therapies (15–17). Weight loss in patients receiving GLP-1 receptor agonists is thought to occur as a result of slowed gastric emptying and increased satiety. In a study of obese patients with accelerated gastric emptying, treatment with exenatide BID for 30 days resulted in slowed gastric emptying and a modest reduction in caloric intake compared to placebo (25).

Cardiovascular Effects

People with type 2 diabetes are at increased risk for cardiovascular compli-

cations; therefore, the cardiovascular effects of antihyperglycemic medications are of interest. Furthermore, U.S. Food and Drug Administration (FDA) recommendations announced in a 2008 call for evidence that therapies for type 2 diabetes do not increase the risk of cardiovascular events such as myocardial infarction (26). Thus, it is necessary to assess cardiovascular outcomes in clinical trials of new antihyperglycemic agents. Intensified, multifactorial treatment to therapeutic goals (targeting glycemic control, blood pressure, lipid levels, and renal function) has been associated with a reduction in cardiovascular and microvascular complications (27).

As reviewed by Saraiva and Sposito (28), a number of findings indicate that GLP-1 receptor agonists do not worsen CVD and may have broader potential cardiovascular benefits in patients with type 2 diabetes. A meta-analysis of 25 studies of GLP-1 receptor agonists showed no increase in major adverse cardiovascular events (including cardiovascular death, nonfatal myocardial infarction, stroke, and acute coronary syndromes and/or heart failure reported as serious adverse events) versus all comparators, with a significant reduction versus placebo (odds ratio 0.506, $P = 0.029$) (29). In a retrospective analysis, patients with type 2 diabetes receiving exenatide ($n = 39{,}275$) were less likely than patients receiving other glucose-lowering treatments ($n = 381{,}218$) to have a CVD event (hazard ratio [HR] 0.81, $P = 0.01$), with CVD-related hospitalization (HR 0.88, $P = 0.02$), or hospitalization for any cause (HR 0.94, $P < 0.001$), despite a greater prevalence of previous ischemic heart disease, obesity, hyperlipidemia, hypertension, and other comorbidities at baseline (30). However, the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial found that the once-daily GLP-1 receptor agonist lixisenatide had a neutral effect on cardiovascular outcomes, neither increasing nor decreasing incidence relative to placebo (31). Additionally, results of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) trial have been announced, indicating a significant reduction in cardiovascular events (defined as cardiovascular death or nonfatal myocardial infarction or stroke) after up to 5 years of treatment with liraglutide versus placebo (13.0 vs. 14.9%, HR 0.87, $P < 0.001$ for noninferiority, $P = 0.01$ for superiority), both in addition to standard of care (32). Similar positive cardiovascular results were reported recently for semaglutide, an investigational GLP-1 receptor agonist administered QW (33). Additional cardiovascular outcomes trials for other GLP-1 receptor agonists are in progress, and results are anticipated in the near future.

Effects on Blood Pressure and Lipid Profiles

GLP-1 receptor agonists have been shown to decrease systolic blood pressure (SBP) and, to a lesser extent, diastolic blood pressure (DBP). In a network meta-analysis of 60 clinical trials, GLP-1 receptor agonists were associated with significant reductions in SBP (ranging from −1.84 mmHg [95% CI −3.48 to −0.20] for dulaglutide to −2.65 mmHg [95% CI −5.19 to −0.24] for albiglutide 30 mg) compared to placebo (34). A significant reduction in DBP compared to placebo was observed only for exenatide BID (−1.08 mmHg [95% CI −1.78 to −0.33]).

Improvements in lipid levels also have been observed during treatment with GLP-1 receptor agonists. A network meta-analysis of 35 clinical trials showed that these agents were associated with significant reductions in LDL cholesterol (weighted mean difference −3.1 mg/dL [95% CI −4.6 to −1.9]) and total cholesterol (−5.0 mg/dL [95% CI −7.3 to −2.7]) versus control (35).

Place in Therapy

According to the AACE/ACE and ADA diabetes treatment algorithms for glycemic control (36,37), GLP-1 receptor agonists are recommended as add-on therapy for patients who do not achieve their A1C target after 3 months of metformin therapy. GLP-1 receptor agonists also are recommended as first-line therapy as an alternative to metformin in patients who cannot tolerate or are contraindicated for metformin. GLP-1 receptor agonists are well suited for early use in type 2 diabetes because they stimulate release of insulin and suppress glucagon secretion only when blood glucose concentrations are elevated; thus, the risk of hypoglycemia is low (38).

Use in Combination Therapy

As dual therapy, GLP-1 receptor agonists are recommended in combination with metformin for patients who do not achieve A1C goals with metformin alone (36). For patients requiring triple therapy, GLP-1 receptor agonists can be combined with metformin and a sodium–glucose cotransporter 2 inhibitor in patients with persistent hyperglycemia. This triple combination is particularly well suited for overweight patients trying to control their weight. Additionally, incretin use with basal insulin may delay the use of bolus (mealtime) insulin with reduced risk of hypoglycemia. This simplified regimen reduces the need for matching mealtime insulin to specific carbohydrate ratios and also helps mitigate the weight gain often seen with insulin use.

Selection and Prescribing Considerations

Patient Considerations

Selecting the most appropriate treatment for an individual patient can help to enhance treatment adherence. A number of patient-specific factors may be relevant to consider, including:

- Treatment history:
  - If initiating GLP-1 receptor agonist therapy early in the course of treatment, after or

with metformin, the patient may have more endogenous insulin secretion and therefore a more robust response.
    - If initiating with insulin or a sulfonylurea, proactive dose reductions of those agents may be considered to avoid hypoglycemia.
- Baseline A1C and glycemic trends and patterns:
    - Patients with elevated glucose levels may not require any dose reduction of other antihyperglycemic agents when initiating GLP-1 receptor agonists.
    - If A1C is modestly elevated or glucose levels are close to target, proactive reductions in the doses of sulfonylureas and insulin may be prudent.
    - Glucose monitoring results will show the greatest impact of short- and intermediate-acting GLP-1 receptor agonists on postprandial glucose levels.
    - Fasting glucose levels will be noticeably reduced with long-acting GLP-1 receptor agonists after a few weeks of treatment.
    - Patients should be advised that they may not have glycemic improvement for 2–4 weeks after initiating treatment with long-acting GLP-1 receptor agonists.
- Renal function:
    - Exenatide BID and QW should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease (ESRD) and should be used with caution in patients with moderate renal impairment (creatinine clearance 30–50 mL/min) or with a history of renal transplantation (13,15).
    - There are limited data on the use of liraglutide in patients with renal impairment; thus, liraglutide should be used with caution in this population (14).
    - Albiglutide, dulaglutide, and lixisenatide may be used without dose adjustment in patients with mild, moderate, or severe renal impairment (estimated glomerular filtration rate 15–89 mL/min/1.73 m^2), and dulaglutide may be used without dose adjustment in patients with ESRD. However, renal function must be monitored in patients with renal impairment who experience severe gastrointestinal adverse effects during treatment with albiglutide, dulaglutide, or lixisenatide because of the potential for dehydration (16–18).
- Frequency of administration:
    - Long-acting GLP-1 receptor agonists should be taken on or around the same day each week. Because of the long half-life of these agents, patients may take the dose up to 3 days before the next injection if they miss the planned day.
- Needle size:
    - GLP-1 receptor agonists are supplied as single- or multi-dose pens, which may include specific needles or, for certain products, require a separate prescription for needles (see Table 1 and the section "Writing the Prescription for a GLP-1 Receptor Agonist"). Needle gauge requirements vary by product but are not believed to be the main factor affecting patient preference (39).
- Insurance coverage and out-of-pocket cost to patients:
    - Insurance coverage and formulary restrictions often factor into which GLP-1 receptor agonist is initially prescribed to patients.
    - Most manufacturers offer programs to reduce copayments (e.g., copayment cards), some with cash value, that may contribute to annual deductibles.

Safety Considerations

- Contraindications to the use of GLP-1 receptor agonists must be considered when selecting a treatment. Labeling for these agents highlight certain rare adverse events that may be associated with them, including thyroid C-cell tumors and pancreatitis.
- No cases of medullary thyroid carcinoma have been reported in clinical trials of GLP-1 receptor agonists; however, based on thyroid C-cell hyperplasia, adenomas, and medullary thyroid carcinomas observed in studies of these agents in mice (40), all of the GLP-1 receptor agonists except exenatide BID and lixisenatide are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2 (14–18).
- GLP-1 receptor agonists should be used with caution in patients with gastroparesis or severe gastroesophageal reflux disease, with careful monitoring and dose adjustments as needed (36).
- The pancreatic safety (particularly with regard to acute pancreatitis) of incretin-based drugs such as GLP-1 receptor agonists has been discussed in recent years. The FDA and the European Medicines Agency concluded that available data were not consistent with a causal association between incretin-based therapies and pancreatitis, but data on the pancreatic effects continue to be monitored (41). Meta-analyses of data from observational studies also do not support an association between incretin use and acute pancreatitis (42,43). Warnings regarding the risk of acute pancreatitis are included in the prescribing information for GLP-1 receptor agonists (13–18). Prescribers should refer to the full prescribing information for these agents when making prescribing decisions.

Dosing Considerations

- Recommended initial doses for GLP-1 receptor agonists currently approved in the United States are summarized in Table 1.
- Starting on lower doses and titrating slowly reduces the risk of nausea and other gastrointestinal effects.
- Except for exenatide QW, doses of GLP-1 receptor agonists may be adjusted based on glycemic control. For liraglutide, it is important to note that the 0.6-mg starting dose is recommended only for the first week to help minimize gastrointestinal adverse events; all patients should titrate to 1.2 mg after the first week to receive therapeutic levels for maximum antiglycemic effect (14).

Writing the Prescription for a GLP-1 Receptor Agonist

- Exenatide BID and liraglutide need an extra prescription for pen needles. Research suggests that shorter needles are adequate to reach subcutaneous tissue and will likely increase patients' acceptance of injections (44–46). Allowing brand exchange may be more cost-efficient for the patient; however, the prescription should be specific on needle length.
- Exenatide QW is available in two formulations, so specification on the prescription is required to use the more patient-friendly pen formulation. Otherwise, the pharmacist may dispense the more cumbersome single-dose trays.
- If samples are available, this will allow patients to have several weeks of therapy to monitor for adverse events and glycemic response before a prescription is written. If samples are not available, a prescription written for 1 month and filled through a local retail pharmacy will allow a patient to have a similar shorter-term experience.
- If the response to treatment is satisfactory, a patient's prescription plan may allow for subsequent prescriptions to be filled by mail-order pharmacies for 3-month cycles, which will provide lower out-of-pocket costs for patients and may honor the copayment cards.

Educating and Advising Patients

Successful diabetes management includes educating patients regarding their specific treatment plan so that they know what to expect from the treatment and how to use it correctly.

Patients being prescribed a GLP-1 receptor agonist should be instructed regarding proper storage and mixing (if needed) of the medication before injection, correct dosage, administration sites, and administration technique. Medication storage and injection preparation and use requirements may differ by product; thus, directions should be reviewed not only with patients receiving a first GLP-1 receptor agonist prescription, but also for those changing medications. Patients should be advised that GLP-1 receptor agonists are not insulin, but some patients may need both a GLP-1 receptor agonist and insulin. Before beginning therapy with a GLP-1 receptor agonist, patients should be advised of potential adverse effects and any tips for mitigating them if they occur. For example:

- Stop eating when you feel full. Reducing food intake may lessen nausea and vomiting. If nausea occurs, it should lessen over time, usually weeks. If nausea and vomiting occur for a prolonged period of time, call the health care provider.
- Injection-site reactions or hypersensitivity are not uncommon. Injection-site nodules may occur with exenatide QW but should dissipate. The exenatide molecule is encased in microspheres that dissipate and become inert after a few weeks.
- Expectations about weight loss should be realistic (~6–8 lb). Greater weight loss may occur, especially if patients begin to feel full, eat less, and exercise.
- If unrelenting abdominal pain occurs, stop the medication and call the health care provider. This may be a sign of pancreatitis.
- Helping patients opt in for companies' persistency programs may help them remember to take injections, get refills, and contact providers if clinical concerns occur.

The most frequently reported treatment-related adverse effects occurring with GLP-1 receptor agonists are gastrointestinal, primarily nausea (occurring in 25–60% of patients in clinical trials), vomiting (5–15%), and diarrhea (10–20%) (47). In general, the long-acting GLP-1 receptor agonists have been associated with lower rates of gastrointestinal adverse events. Importantly, the incidence of nausea decreases with time. GLP-1 receptor agonists do not increase the risk of hypoglycemia relative to placebo (48); however, agents such as insulin or sulfonylureas increase hypoglycemia risk compared to placebo (48) and when used concomitantly with GLP-1 receptor agonists (13–18).

Because GLP-1 receptor agonists are therapeutic peptides, treatment with these agents has the potential to lead to the development of anti-drug antibodies. Generally, low antibody titers are detected in a minority of patients, and higher titers develop in a much smaller proportion of patients (49–52). Anti-drug antibodies could reduce therapeutic efficacy, although such an effect typically is observed only in the presence of higher-titer antibodies. In addition, there is the potential for an increased incidence of hypersensitivity reactions such as injection-site reactions.

As noted above, meta-analysis findings suggest no increased risk of major adverse cardiovascular events in patients receiving GLP-1 receptor agonists, and there is some suggestion of potential benefit (29). The find-

ings of the ELIXA outcomes study were neutral with respect to cardiovascular outcomes (31), whereas liraglutide demonstrated advantages versus placebo in the LEADER trial (32). Other large cardiovascular outcomes trials are being conducted to evaluate the cardiovascular safety of exenatide QW (EXenatide Study of Cardiovascular Event Lowering [EXSCEL; NCT01144338]; planned completion April 2018) (53), albiglutide (HARMONY Outcomes [NCT02465515]; planned completion May 2019), and dulaglutide (REsearching Cardiovascular Events with a Weekly INcretin in Diabetes [REWIND; NCT01394952]; planned completion April 2019).

Conclusion

Agents in the GLP-1 receptor agonist class are effective treatment options for patients with type 2 diabetes, achieving reductions in A1C and body weight as monotherapy or as an add-on to other antihyperglycemic therapies, including insulin. Helping patients establish realistic expectations and providing education about how the medication works are important to help ensure desired outcomes.

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Duality of Interest

Ms. Hinnen is an advisor for AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi and has participated in speakers' bureaus for Eli Lilly, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

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