Optimizing Outcomes for GLP-1 Agonists

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The management of type 2 diabetes mellitus and, in particular, blood glucose levels can be complex and challenging for physicians and patients. Many patients are frustrated with the agents currently available because they have associated limitations of weight gain, hypoglycemia, and tolerability issues. Advantages of glucagon-like peptide-1 (GLP-1) agonists include their efficacy in lowering blood glucose levels, their lack of association with weight gain, and their indirect association with weight loss. Patients likely to benefit from GLP-1 agonist therapy are those in the early stages of the disease and those in need of sufficient benefit from an agent with good efficacy. Setting appropriate expectations for patients is important, as well as explaining the significance of glucose control and reminding patients that this is the main goal of therapy. Patients (and physicians) who have concerns about hypoglycemia can be reassured that GLP-1 agonists work only in the presence of hyperglycemia. Longer-acting GLP-1 agonists are dosed less frequently, appear to be associated with less nausea, and may be associated with better rates of adherence than shorter-acting agents. When initiating therapy with GLP-1 agonists, doses should be gradually escalated to minimize gastrointestinal adverse effects. The dose of a sulfonylurea may need to be lowered if a GLP-1 agonist is added. A review of possible adverse effects, contraindications, dosing and administration techniques, and expected benefits of therapy is provided in the present article to optimize success rates with this new class of agents.

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The management of type 2 diabetes mellitus and, in particular, blood glucose levels can be complex and challenging for both physician and patient. Appropriate control of diabetes provides meaningful microvascular risk reduction, yet patients with type 2 diabetes commonly languish at unsatisfactory levels of glycated hemoglobin (HbA_{1c}) for protracted periods.[1] Many patients fail to achieve glycemic goals with initial monotherapy, and, of those who achieve recommended goals, few consistently maintain these targets over 3 years.[2] Both specialists and generalists who treat patients with diabetes may exhibit "clinical inertia"—the failure to appropriately advance or titrate therapy to achieve glycemic goals. For myriad reasons, compared with specialists, primary care physicians have a tendency to treat patients with diabetes less aggressively. Primary care physicians are also less likely to use insulin therapy and are slower to intensify therapy.[3]

Many patients are frustrated with the antihyperglycemic agents currently available because of potential adverse effects (eg, weight gain, hypoglycemia) and tolerability issues. Patient adherence to a diabetes regimen is a clinically significant challenge in the appropriate management of diabetes. Half of patients with diabetes stay on their medication for 6 months or less.[4] Nonadherence is associated with elevated glucose levels, which may lead to increased risk of serious diabetes-related complications: neuropathy and amputation, nephropathy and renal failure, retinopathy and blindness, and cardiovascular deterioration.[5,6] Patient concern over antihyperglycemic medication has been associated with a low level of health literacy and with patient dissatisfaction regarding access to information about medication. This can be remedied with consistent patient evaluation, counseling, answering questions, and asking patients to restate key points.[7] Patients with type 2 diabetes may experience anxiety over possible adverse

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effects, may be fearful of developing a dependency on medication, and may worry about medication costs.[8] It is important for clinicians to approach patients as individuals and to elicit and acknowledge patients' concerns about current and future medications. A shared decision-making approach to treatment helps improve diabetes care, achieve better glycemic control, and thereby improve patient outcomes.

The availability of glucagon-like peptide-1 (GLP-1) agonists is an important addition to treatment options for patients with type 2 diabetes. These agents can be used alone or in combination with commonly available oral antihyperglycemic agents. The fear of hypoglycemia and weight gain associated with most of the available treatments for patients with type 2 diabetes may affect the attitudes of providers and patients toward therapy intensification. Because GLP-1 agonists lack these effects, they may be useful as add-on medications to established treatments or as alternative medications. In the present article, I review several considerations for optimizing treatment success.

Candidates for GLP-Agonist Therapy

Current treatment algorithms highlight the use of GLP-1 agonists, primarily as part of combination treatment strategies, and target patients who are overweight or at risk for hypoglycemia.[9-11] Patients cite the fear of developing hypoglycemia as their major concern about antihyperglycemic therapies. Patients with this fear can be reassured that GLP-1 agonists work in a glucose-dependent manner (ie, only when glucose levels are elevated) and are associated with a low risk of hypoglycemia.

Advantages of GLP-1 agonists include their efficacy in lowering blood glucose levels (either alone or in combination with other commonly used antihyperglycemic therapies), their lack of association with weight gain, and their indirect association with weight loss. Patients should be made aware of these potential benefits.

Patients likely to benefit from GLP-1 agonist therapy are those in the early stage of the disease and those in need of sufficient benefit from an agent with good efficacy. Patients who can benefit from GLP-1 agonist monotherapy are those who are not good candidates for metformin or a sulfonylurea. Other patients who may benefit from therapy include those with occupations in which having hypoglycemia is especially dangerous (eg, truck drivers); overweight patients who want to lose weight, particularly those with suboptimal glycemic control with oral therapy; and patients who are reluctant to transition to insulin because of possible weight gain, hypoglycemia, or both.[9]

Choosing Between Incretin-Based Agents: Patient Considerations

Patients may wonder about the differences between the 2 major classes of incretin-based therapies, GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. The most obvious difference is method of administration (subcutaneous injection vs oral). Other relevant differences are summarized in *Figure 1*.

Parameter	GLP-1 Agonists	DPP-4 Inhibitors
Administration	Subcutaneous injection	Oral
Risk of hypoglycemia	Low	Low
Effects on gastric emptying	Reduced	Nominal
Effects on appetite	Reduced	Nominal
Effects on body weight	Weight loss	Weight neutrality
Tolerability	Gastrointestinal adverse effects (nausea, vomiting)	Generally well tolerated (minimal side effects)

Figure 1. *Relative effects of glucagon-like peptide-1 (GLP-1) agonists vs dipeptidyl peptidase-4 (DPP-4) Inhibitors.*

Both classes of agents work by glucose-dependent mechanisms (only in the presence of hyperglycemia), associating them with a low risk of hypoglycemia. Neither GLP-1 agonists nor DPP-4 inhibitors are associated with weight gain. While DPP-4 inhibitors are considered weight neutral, GLP-1 agonists are consistently associated with weight loss. The weight loss is generally slow and progressive over time[12,13] because GLP-1 agonists have slow gastric-emptying and satiety effects in the central nervous system. In some cases, weight loss can be dramatic, but not all patients will lose weight. Generally, patients with a greater body mass index (BMI) tend to lose the most weight (*Figure 2*).[14] Weight gain can be a significant barrier to intensifying treatment for patients with type 2 diabetes. Many patients are anxious about their weight, and the importance of losing weight has been stressed to them. The fear of increasing weight and the immediate associated health and cosmetic effects may override the patient's fear of long-term complications from diabetes.[15] Setting appropriate expectations for patients is important, as are explaining the significance of glucose control and reminding patients that such control is the main goal of therapy.

Overall characteristics of longer-acting GLP-1 agonists (eg, once-daily liraglutide) may make them attractive to patients with type 2 diabetes. These medications typically lead to less nausea, improved patient adherence, and improved cardiovascular risk factors (lower blood pressure, improvements in lipid profiles). They also appear to lower HbA_{1c} levels more than short-acting exenatide, probably because they have effects on both fasting plasma glucose and postprandial glucose levels. In a recent meta-analysis, patients receiving liraglutide showed greater reduction in HbA_{1c} levels in comparison with placebo than those on exenatide or sitagliptin (*Table 1*).[16] In the only head-to-head comparison reported so far between exenatide and liraglutide, a superior glucose-lowering effect was observed with liraglutide, and less nausea was reported.[17,18]

When presented with different options for GLP-1 agonist treatments,

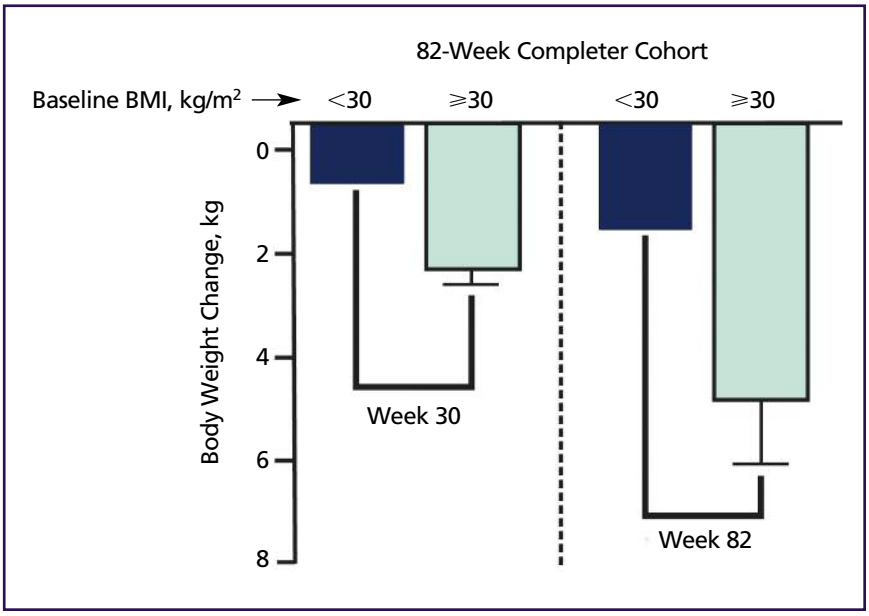

Figure 2. *Change in body weight with exenatide stratified by baseline body mass index (BMI). Baseline BMI less than or BMI greater than or equal to 30 kg/m² at weeks 30 and 82 for the 82-week completer cohort (n=92) and the 82-week total cohort (n=150) (mean [standard deviation]). Adapted with permission from Ratner et al.*[14]

patients say they value glucose-lowering ability, low risk of nausea, low risk of hypoglycemia, and convenience in dosing.[19] Dosing information for exenatide and liraglutide are provided in *Table 2*.

When initiating therapy with a GLP-1 agonist, the dose should be escalated gradually to minimize severity of the most common adverse effects, which are gastrointestinal in nature. Less than 5% of patients withdraw from GLP-1 agonist therapy because of these effects.[20] If nausea or vomiting becomes problematic with a GLP-1 agonist, the dose can be reduced temporarily until tolerability improves. If such effects are especially troublesome to the patient, suggest that he or she eat slowly and remain on the lower dose for another month. If the GLP-1 agonist being used is exenatide, suggest that the patient take it closer to mealtime. Inform the patient about these effects in advance so he or she is not surprised. The longer-acting GLP-1 agonists appear to have fewer gastrointestinal adverse effects.[21] Patients can also be told that weight loss occurs with GLP-1 agonists irrespective of gastrointestinal adverse effects (*Figure 3*).[22]

Exenatide is started at a dose of 5 mg twice a day for 30 days and is titrated to 10 mg twice a day if the lower dose is tolerated (usually after 1 month). Exenatide should be injected within 60 minutes of morning and evening meals, at least 6 hours apart.[23] Exenatide should not be taken after a meal. If a dose of exenatide is missed, the patient should skip the missed dose and resume the usual dosing schedule with the next scheduled dose.

Many patients with type 2 diabetes would likely wish to limit the number of injections taken. Liraglutide is a longer-acting GLP-1 agonist that is dosed subcutaneously, once daily. Injections of liraglutide can be administered at any time of day, regardless of relationship to meals, although patients should be encouraged to take the medication consistently at about the same time each day. If a dose of liraglutide is missed and it is less than 12 hours from when it should have been taken, the patient may take the dose. However, if it has been more than 12 hours from the usual time of administration, then it is preferable to omit the dose and restart therapy at the next scheduled time. Patients should be counseled not to increase the dose on the following day to "make up" for the missed dose.

In most cases, patients start with a low dosage (0.6 mg once daily) during the first week of treatment. Although this amount is usually too low to be effective, it prepares the body for higher doses and reduces the risk of adverse effects. After the first week, the dose may be increased to 1.2 mg/d or, if necessary, 1.8 mg/d to achieve HbA_{1c} target. Daily doses higher than 1.8 mg are not recommended.[20] The prefilled disposable pen for subcutaneous injection contains 18 mg of liraglutide in 3 mL; the pen device allows the dose to be selected easily (0.6, 1.2, or 1.8 mg). Thirty-day supplies are available as a 2-pen box for the 1.2-mg dose and a 3-pen box for the 1.8-mg dose.[20] Liraglutide pens need only be primed once before use; priming before each dose will result in the patient running out of the medication prematurely.[20] Liraglutide pens in use can be stored at room temperature or refrigerated but should be discarded after 30 days.[20] Patients will need a prescription for needles; they may use needles up to 8 mm long and as thin as 32 gauge. Injections can be given in the abdomen, thigh, or upper arm, and the site can be changed as needed.[20]

Table 1.
Treatment of Patients With Type 2 Diabetes Mellitus

Medication	Number of RCTs	Change From Baseline (metaregression) HbA_{1c} level, %	Weight, kg
Sitagliptin	12	–0.79*	+0.6*
Exenatide	8	–0.75*	-1.1*
Liraglutide	7	–1.03*	-0.82†

* $P<.001$
† $P=.142$

Source: Adapted from Fakhoury.[16]

Table 2.
Dosage and Administration of GLP-1 Agonists

Characteristic	Exenatide	Liraglutide
Starting Dose	5 μg	0.6 mg*
Dose Titration	After 1 month, may increase to 10 μg if tolerated	After 1 week, increase to 1.2 mg, may increase to 1.8 mg if needed and tolerated
Dosing Frequency	Twice a day	Once a day
Timing of Doses	0-60 minutes before AM and PM meals; to reduce nausea, take closer to meal; maximum satiety at 1 hour before meal	Without regard to mealtime
Missed Doses	Skip the missed dose and resume the usual dosing schedule with the next scheduled dose; do not double the dose to "catch up"	☐ If a dose of liraglutide is missed and it is <12 hours from when you should have taken it: Take the dose ☐ If a dose of liraglutide is missed and it is >12 hours from when should have taken it: Do not take an extra dose ☐ Do not increase the dose on the following day to "make up" for the missed dose
Dosing in Patients With Renal Impairment	Should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation; Caution should be applied when initiating or escalating doses from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 mL/min to 50 mL/min)	No dosage adjustment recommended, but little data available
Drug Interactions	Interactions may occur due to effects on gastric emptying, relevant for drugs with a narrow therapeutic index†,‡; In patients taking warfarin, prothrombin time should be monitored more frequently after initiation or alteration of exenatide therapy	Low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding; Interactions may occur due to effects on gastric emptying, relevant for drugs with a narrow therapeutic index†
If Added to Sulfonylurea Therapy	Consider reducing dose of sulfonylurea	Consider reducing dose of sulfonylurea

* Although this amount is usually too low to be effective, it prepares the body for higher doses and reduces the risk of side effects.
† Examples include antibiotics, contraceptives, and digoxin.
‡ For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take such drugs at least 1 hour before exenatide injection.

Concerns

Use in Patients With Renal Impairment

Although exenatide was generally well tolerated in patients with mild and moderate renal impairment, it was not well tolerated in those with end-stage renal disease or in those who had an increased incidence of nausea and vomiting.[24] Based on recent pharmacokinetic studies, patients with type 2 diabetes and mild renal impairment may use standard treatment regimens of liraglutide.[24,25] Currently, there is only limited information regarding use of liraglutide in patients with more severe renal disease.[25]

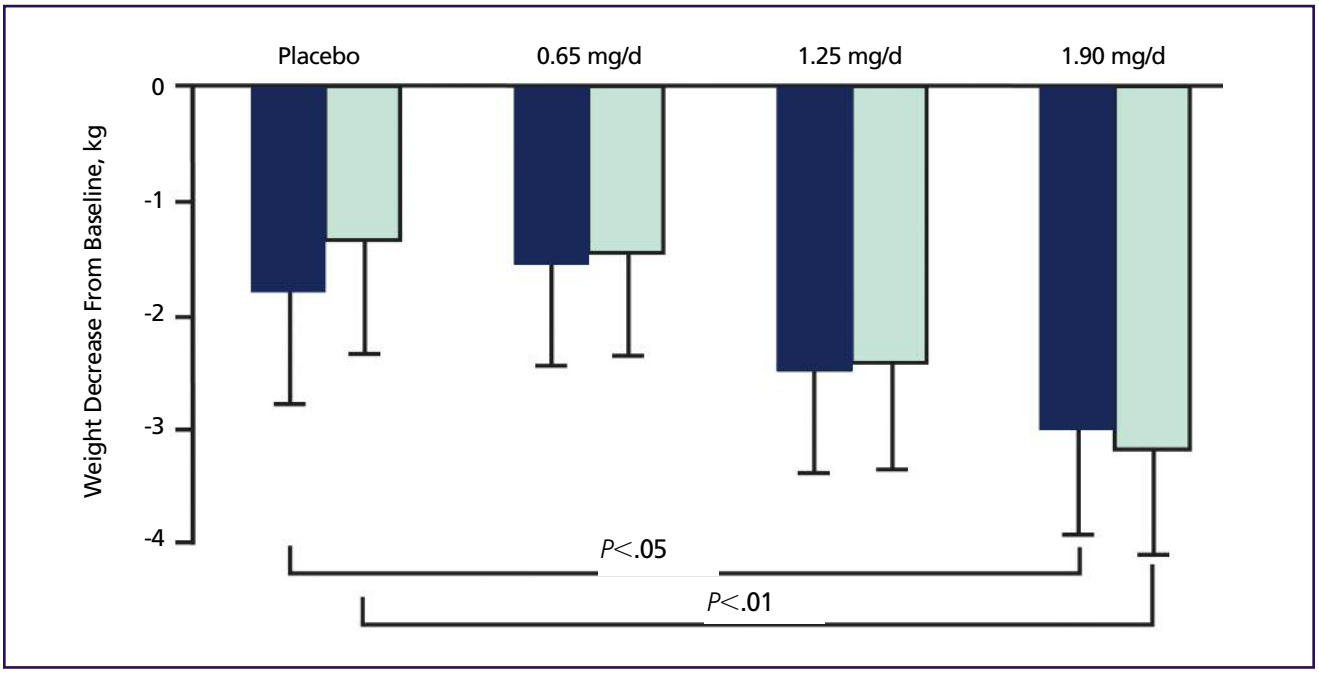

Figure 3. *Change in body weight with liraglutide.*[22]

Drug Interactions

Interactions from drugs such as antibiotics, contraceptives, and other narrow threshold drugs with GLP-1 agonists result from the slowing of gastric emptying, which affects absorption patterns. Of specific relevance to patients with diabetes is an increased risk of sulfonylurea-related hypoglycemia when GLP-1 agonists are started. The dose of the sulfonylurea may need to be reduced when a GLP-1 agonist is added to this therapy.[25]

Other

Although there has been concern about pancreatitis with incretin-based therapies, data from safety surveillance systems show no evidence of pancreatitis being caused by these agents.[26] Diabetes itself is associated with twice the risk of pancreatitis; obesity is also a risk factor for pancreatitis.[27] Moreover, diabetes is associated with hypertriglyceridemia and gallstones, both of which may cause pancreatitis. Other medications often used in patients with type 2 diabetes may cause pancreatitis, such as sulfonylureas, statins,[28] fibrates,[29] and antihypertensive agents (including thiazides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers).[30] Patients with diabetes should be counseled about the symptoms of pancreatitis. These include persistent severe abdominal pain that can radiate to the back, which may or may not be accompanied by nausea and vomiting. Exenatide and liraglutide should be stopped if signs of pancreatitis develop and should be used with caution in patients who have a history of the disease.[20,23]

In rodents, but not primates, liraglutide has been associated with an increased risk of medullary thyroid cancer.[31] To minimize risk, liraglutide is therefore contraindicated in patients with multiple endocrine neoplasia syndrome type 2 or a personal or family history of medullary thyroid cancer.[20]

Take-Home Counseling Points With GLP-1 Agonists

The benefits of GLP-1 agonist therapy can be explained to patients in terms of a reduced HbA_{1c} and the associated reduced risk of future health complications. This therapy, combined with better food choices, can increase patients' opportunity for weight loss, which may lead to lower cardiovascular risk because of modest improvements in blood pressure and lipid profiles. Patients should be proactively informed about the risk of nausea and other gastrointestinal adverse effects with GLP-1 agonists. Physicians should stress that GLP-1 agonists are not insulin and do not replace insulin. (Insulin therapy may someday still be needed as β-cell function continues to decline). Make sure patients are aware of the rare but serious risks of pancreatitis. If selecting liraglutide therapy, ask about family or personal history of thyroid cancer and discuss the black-box warning with appropriate context for those patients who are, indeed, viable candidates for this drug.

Conclusion

The availability of GLP-1 agonists for the treatment of patients with type 2 diabetes is creating opportunities for meaningful improvement in the rate of glycemic control for appropriate patients. Osteopathic physicians are encouraged to learn more about these agents and how they can be successfully incorporated into treatment strategies to improve patient outcomes.

Case Presentation

Charlie is a 55-year-old African-American man who was diagnosed with type 2 diabetes approximately 12 months ago. Of average height, he is modestly obese with a body mass index

(BMI) of 30.7. His baseline HbA_{1c} level was 8.5% before therapy was initiated. Lifestyle management and metformin (1000 mg twice daily) taken for 3 months from the time of diagnosis resulted in an HbA_{1c} level of 7.8%. A thiazolidinedione was added at 3 months but was later discontinued because of edema and weight gain. Glimepiride (8 mg daily) was added to the metformin, but Charlie's target HbA_{1c} goal of less than 7.0% still was not reached. Exenatide was added and the glimepiride dose was reduced.

At a 1-month follow-up appointment after initiation of a GLP-1 agonist, Charlie's weight had decreased to 215 lb (BMI, 30), and his HbA_{1c} had improved to 7.2% (from 7.8%). He reported no symptoms of hypoglycemia but stated that he had been experiencing mild nausea since increasing the dose of his GLP-1 agonist. He was switched to once-daily liraglutide, which was slowly titrated to the maximum dose of 1.8 mg. Three months later, he is congratulated on achieving his target HbA_{1c} goal of less than 7.0%. His weight is now 210 lb (BMI, 29.3). Besides taking his medication, he is eating better and exercising regularly.

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