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Integrating Incretin-Based Therapy into Type 2 Diabetes Management

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LEARNING OBJECTIVES

1. Explain the concept of the incretin effect and describe defects in incretin secretion and incretin action that occur in type 2 diabetes mellitus (T2DM)
2. Provide an overview of the rationale and role of incretin-based therapy as described in current practice guidelines for the management of patients with T2DM
3. Compare the efficacy, safety, and tolerability of the incretin-based therapies currently available
4. Describe strategies to optimize incretin-based therapy

TARGET AUDIENCE

Primary care physicians and clinicians with an interest in diabetes treatment and management

SPONSOR DISCLOSURE STATEMENT

Dr Stephen Brunton discloses that he is on the advisory boards for Abbott, Boehringer-Ingelheim, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva. He is on the speakers' bureaus for Boehringer-Ingelheim, Janssen, Kowa, Lilly, Novo Nordisk, and Teva.

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Insulin resistance and pancreatic β-cell dysfunction are well-established as the two core pathophysiologic defects in patients with type 2 diabetes mellitus (T2DM). In 2009, DeFronzo[1] proposed that 6 other defects also contribute to glucose intolerance in T2DM. Among this "ominous octet" of defects, the role of the incretin hormones in the gastrointestinal system has been increasingly recognized. Known as the incretin effect, this phenomenon may be responsible for up to 70% of insulin secretion in response to oral glucose or a meal in healthy individuals.[2] Of the incretin hormones, glucagon-like peptide-1 (GLP-1) is particularly important as postprandial levels of GLP-1 are decreased in patients with impaired glucose tolerance or T2DM.[3] Since GLP-1 affects glucose homeostasis by reducing the fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels,[4] pharmacologic agents that raise the level or activity of GLP-1 have been developed. This article compares the 7 agents currently available that act on the incretin system, emphasizing strategies to improve patient self-management with the GLP-1 receptor (GLP-1R) agonists.

Overview of GLP-1R Agonists and DPP-4 Inhibitors

The GLP-1R agonists increase the activity of GLP-1 by directly binding to the GLP-1 receptor. In contrast, the dipeptidyl peptidase-4 (DPP-4) inhibitors inhibit the enzymatic degradation of endogenous GLP-1, thereby increasing the plasma level of active endogenous GLP-1. As a consequence of these differences in mechanism of action, the GLP-1R agonists have a greater impact than the DPP-4 inhibitors on glycemic and non-glycemic effects **(TABLE 1)**.[5-28] Two differences that are particularly important clinically include a greater reduction of the glycated hemoglobin (A1C) level and a greater weight loss with the GLP-1R agonists than with the DPP-4 inhibitors.

An important benefit of the GLP-1R agonists and DPP-4 inhibitors is a low incidence of hypoglycemia, likely because incretin hormones stimulate insulin secretion and reduce glucagon secretion in the presence of hyperglycemia. As monotherapy, the incidence of hypoglycemia with currently available GLP-1R agonists is 4% to 9% with exenatide for twice-daily administration (BID),[29,30] 5% with exenatide for once-weekly administration (QW),[16] and 0% to 12% with liraglutide.[7,8] For monotherapy with the DPP-4 inhibitors, the incidence of hypoglycemia is 2% to 3% with alogliptin,[26] 0% with linagliptin,[31] 0% with saxagliptin,[20,25] and 1% to 2% with sitagliptin.[18,19,24] However, when a GLP-1R agonist or DPP-4 inhibitor

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is combined with a sulfonylurea, the incidence of hypoglycemia increases several-fold.[5,9,14,15,31-34] Consequently, reducing the dose of the sulfonylurea is recommended with this combination.

The dosing and use of GLP-1R agonists and DPP-4 inhibitors in special populations are outlined in **TABLE 2**.[35-41] It should also be noted that the safety and effectiveness in children of all GLP-1R agonists and DPP-4 inhibitors have not been demonstrated.

As relatively new products for the treatment of patients with T2DM, a full appreciation of the safety of the incretin-based therapies in wide clinical use is only beginning to emerge. Clinical trials and postmarketing reports have raised the possibility that the GLP-1R agonists and DPP-4 inhibitors may increase the risk of acute pancreatitis. Investigations to assess a possible relationship have yielded conflicting results, in part because patients with T2DM, regardless of treatment, have a nearly 3-fold higher risk of pancreatitis compared with patients without diabetes.[42] Several retrospective analyses of administrative databases have been conducted to assess a possible relationship between incretin-based therapies and pancreatitis. In one involving nearly 88 000 patients followed for 1 year, there was a similar risk of pancreatitis with exenatide, sitagliptin, metformin, and glyburide.[43] Analysis of another database (N = 786 656) showed the incidence rate to be 5.7 cases/1000 patient-years for exenatide BID, 5.6 for sitagliptin, and 5.6 for patients with T2DM treated with metformin, sulfonylurea, or thiazolidinedione.[44] A third analysis by Singh et al[45] examined the health records of 1269 patients hospitalized with acute pancreatitis and found that current and recent (within 2 years) use of a GLP-1R agonist was associated with an increased risk of acute pancreatitis compared to matched controls (odds ratio was 2.24 for current use and 2.01 for recent use). Publication of this analysis was followed 2 days later by a joint statement from the American Association of Clinical Endocrinologists/American Diabetes Association (AACE/ADA) stating that the analysis by Singh et al "does not provide the basis for changing treatment in people with diabetes."[46] As noted by the AACE/ADA joint statement, 9 prospective, controlled trials of GLP-1R agonist-based therapy involving over 65 000 subjects are ongoing and should provide answers to this and other important safety questions.

Case Study

KB is a 46-year-old woman diagnosed with T2DM 4 years ago. She had a good response to lifestyle intervention combined with metformin, which lowered her A1C from 8.8% to 7.5% over 5 months. The addition of pioglitazone 15 mg once daily (QD) further reduced her A1C to 6.7%. One year after diagnosis, her vital signs and lipid profile remained within normal limits and she had no evidence of cardiovascular disease.

About a year-and-a-half ago, KB was laid off from work, causing her to become severely depressed. Her level of physical activity quickly diminished and she began to watch television most of the day with frequent snacking. Treatment with combination antidepressant therapy has had little impact on her depression. She has continued to be reasonably adherent with her medications through continued health insurance through her husband's employer.

Current visit:

- A1C, 8.2%
- Vital signs: within normal limits; blood pressure (BP), 146/88 mm Hg

TABLE 1 Overview of GLP-1R agonists and DPP-4 inhibitors[5-28]

GLP-1R Agonists	DPP-4 Inhibitors
Subcutaneous Injection • Exenatide twice-daily (Byetta) • Exenatide once-weekly (Bydureon) • Liraglutide once-daily (Victoza)	Oral Ingestion (once-daily) • Alogliptin (Nesina) • Linagliptin (Tradjenta) • Saxagliptin (Onglyza) • Sitagliptin (Januvia)
Resists degradation by DPP-4 enzyme →Level of GLP-1 activity ~60-70 pmol/L	Inhibits DPP-4 enzyme → Level of active GLP-1 ~10 pmol/L
Direct binding to, and stimulation of, GLP-1 receptor	Extends elimination half-life of endogenous GLP-1
Glycemic Effects • ↑Insulin secretion (glucose-dependent) • ↓Glucagon secretion (glucose-dependent)	Glycemic Effects • ↑Insulin secretion (glucose-dependent) • ↓Glucagon secretion (glucose-dependent)
Food and Digestive Effects • Promotes satiety • ↓Caloric intake • ↓Gastric emptying rate	Food and Digestive Effects • None
Effects as Monotherapy • A1C level ↓ 0.4%–2.0% • Weight ↓ 1–4 kg • Hypoglycemia: low risk	Effects as Monotherapy • A1C level ↓ 0.4%–0.9% • Weight ↓ 0.2–0.9kg • Hypoglycemia: low risk
Most Common Adverse Events • Transient GI events (eg, nausea, diarrhea), headache	Most Common Adverse Events • Nasopharyngitis, headache

A1C, glycated hemoglobin; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1R agonist, GLP-1 receptor agonist.

- Weight, 92.3 kg; body mass index (BMI), 34 kg/m^2 (27 kg/m^2 2 years ago)
- Physical examination: 1+ edema of her hands and feet
- Estimated creatinine clearance, 74 mL/minute; no evidence of albuminuria
- Lipids: total cholesterol, 224 mg/dL; low density lipoprotein-cholesterol (LDL-C), 136 mg/dL; high density lipoprotein-cholesterol (HDL-C), 46 mg/dL; and triglycerides, 208 mg/dL

Recognizing that KB's unresolved depression is the basis for her changed health status, KB's primary care provider (PCP) plans to refer her to a psychiatrist for intensified treatment of her depression. A visit with the team's dietician is also scheduled. Noting the elevated BP and edema, KB's PCP decides to discontinue the pioglitazone. She elects to defer starting antihypertensive therapy for 3 months to see if KB's BP might decrease with the discontinuation of the pioglitazone and to not adversely affect KB's adherence with her glucose-lowering medications. The PCP decides to continue the metformin, but discusses with KB changes to her glucose-lowering medications.

- A sulfonylurea is considered because of its low cost and efficacy in lowering the blood glucose, although short durability is a concern as are the propensity for weight gain and hypoglycemia.
- An alpha-glucosidase inhibitor, bromocriptine, or colesevelam are considered, but in light of their modest glucose-lowering efficacy, are not good options.
- Basal insulin would provide the desired reduction in the blood glucose level, but further weight gain is undesirable. In addition, the need for self-injection and hypoglycemia may be limitations.

The PCP also discusses the 2 groups of incretin-based therapy, noting that the GLP-1R agonists promote weight loss and are given by self-injection, while the DPP-4 inhibitors have no appreciable effect on weight and are given orally. The PCP considers the relative glycemic and nonglycemic effects of the GLP-1R agonists and DPP-4 inhibitors.

Head-to-Head Clinical Trials of GLP-1R Agonists vs DPP-4 Inhibitors

Exenatide BID vs Sitagliptin

The glycemic and nonglycemic effects of exenatide BID and sitagliptin have been compared as add-on therapy in patients with T2DM inadequately controlled with metformin.[47] Patients received either exenatide 5 mcg BID for

TABLE 2 Use of GLP-1R agonists and DPP-4 inhibitors in special populations[35-41]

	Kidney Dysfunction/↓CrCl (mL/min)	Elderly	Pregnant	Lactating
GLP-1R Receptor Agonists				
Exenatide twice-daily	50-80: no change in dose	No effect of age on safety or effectiveness; use caution	Category C	Discontinue nursing or discontinue GLP-1R agonist
Exenatide once-weekly	30-50: caution <30: contraindicated			
Liraglutide	No change in dose; use with caution	No effect of age on safety or effectiveness		
DPP-4 Inhibitors				
Alogliptin	≥60: 25 mg QD 30-59: 12.5 mg QD <30: 6.25 mg QD	No effect of age on safety or effectiveness; no change in dose	Category B	Use caution
Linagliptin	No change in dose			
Saxagliptin	>50: no change in dose ≤50: 2.5 mg QD	No effect of age on safety or effectiveness; use caution		
Sitagliptin	≥50: no change in dose 30-49: 50 mg QD <30: 25 mg QD			

CrCl, creatinine clearance; DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor, QD, once daily.

1 week followed by 10 mcg BID for 1 week or sitagliptin 100 mg QD for 2 weeks. At the end of these 2 weeks, patients were crossed over to the other therapy. After 2 weeks, the 2-hour PPG was significantly lower in the exenatide BID group compared with sitagliptin (133 mg/dL vs 208 mg/dL; $P < .0001$). Following crossover, the 2-hour PPG decreased –76 mg/dL in patients switched to exenatide BID and increased 73 mg/dL in patients switched to sitagliptin. Similar reductions in FPG were observed (–15 mg/dL, exenatide BID vs –19 mg/dL, sitagliptin). Compared to sitagliptin, exenatide BID significantly ($P < .05$) improved insulin secretion, improved β-cell function, reduced postprandial glucagon secretion, slowed gastric emptying rate, reduced total caloric intake, and reduced postprandial triglyceride. Nausea occurred in 34% of patients treated with exenatide BID and 12% of patients treated with sitagliptin, with all episodes of mild or moderate intensity.

Exenatide QW vs Sitagliptin

In patients with T2DM inadequately controlled with metformin, patients were randomized to double-blind treatment with exenatide 2 mg QW, sitagliptin 100 mg QD, or pioglitazone 45 mg QD.[12] The reductions in the A1C were –1.5% and –0.9% in the exenatide QW and sitagliptin patients, respectively, at 26 weeks ($P < .0001$). Reductions in FPG were significantly greater with exenatide QW than sitagliptin (–32 mg/dL vs –16 mg/dL, respectively; $P < .05$). Changes in body weight were –2.3 kg with exenatide QW and –0.8 kg with sitagliptin ($P < .001$). The reduction in systolic BP was significantly greater in patients treated with exenatide QW than in patients treated with sitagliptin. Changes in total cholesterol, LDL-C, and HDL-C were not significantly different between exenatide QW and sitagliptin. Significant improvements in all 5 weight-related domains of quality of life were observed with exenatide QW and sitagliptin. The following adverse events occurred in patients treated with exenatide QW or sitagliptin, respectively: nausea (24% vs 10%), diarrhea (18% vs 10%), minor hypoglycemia (1% vs 3%), and injection site reaction (10% vs 7%). Diarrhea was the most frequent cause of study withdrawal, occurring in 2 patients in each group.

Liraglutide vs Sitagliptin

Adults with T2DM inadequately controlled with metformin were randomized to open-label treatment with liraglutide 1.2 mg or 1.8 mg QD or sitagliptin 100 mg QD for 26 weeks.[48] From a mean A1C 8.4% to 8.5% at baseline, reductions in A1C were –1.24% with liraglutide 1.2 mg, –1.50% with liraglutide 1.8 mg, and –0.90% with sitagliptin ($P < .0001$ vs liraglutide 1.2 mg and 1.8 mg). Significantly more patients treated with liraglutide achieved A1C < 7.0% ($P < .0001$). Reductions in FPG were –34 mg/dL and –39 mg/dL for liraglutide 1.2 mg and 1.8 mg, respectively, and –15 mg/dL for sitagliptin ($P < .0001$ vs liraglutide 1.2 mg and 1.8 mg). Mean weight loss was –2.86 kg and –3.38 kg for liraglutide 1.2 mg and 1.8 mg, respectively,

and –0.96 kg for sitagliptin (both $P < .0001$). Some measures of pancreatic β-cell function showed significantly greater improvement with liraglutide than sitagliptin, while others showed comparable improvement. Minimal changes were observed in systolic and diastolic BP and the lipid profile. Generally, similar improvements were observed in treatment satisfaction in all 3 groups. Nausea was experienced by 21% and 27% of patients treated with liraglutide 1.2 mg or 1.8 mg, respectively, and 5% of patients treated with sitagliptin. While nausea was more frequent with liraglutide, it lasted for a shorter period, as the median duration of nausea was 13 days, 8 days, and 26 days, respectively. Major hypoglycemia occurred in 1 patient treated with liraglutide 1.2 mg. Minor hypoglycemia occurred at rates of 0.178 episodes/patient-year with liraglutide 1.2 mg, 0.370 episodes/patient-year with liraglutide 1.8 mg, and 0.106 episodes/patient-year with sitagliptin.

In a 26-week extension wherein patients continued the same treatment, the results were largely the same as during the initial 26 weeks. Significantly greater reductions in A1C persisted with liraglutide 1.2 mg and 1.8 mg (–1.29% vs –1.51%) compared with sitagliptin (–0.88%; $P < .0001$ vs liraglutide 1.2 mg and 1.8 mg).[49] Significantly more patients achieved A1C <7.0% at 52 weeks with liraglutide 1.2 mg (43.7%) and liraglutide 1.8 mg (56.0%) than with sitagliptin (22.0%) ($P < .0001$ vs liraglutide 1.2 mg and 1.8 mg). FPG reductions from baseline at week 52 were –31 mg/dL for liraglutide 1.2 mg, –37 mg/dL for liraglutide 1.8 mg, and –11 mg/dL for sitagliptin ($P < .0001$ vs liraglutide 1.2 mg and 1.8 mg). Changes in β-cell function, BP, and lipid profile were similar to those observed from baseline through 26 weeks. Mean weight loss was –2.78 kg, –3.68 kg, and –1.16 kg for liraglutide 1.2 mg or 1.8 mg and sitagliptin, respectively ($P < .0001$ vs liraglutide 1.2 mg and 1.8 mg). No major hypoglycemia episodes occurred during the extension. Rates of minor hypoglycemia were 0.143 episodes/patient-year, 0.154 episodes/patient-year, and 0.137 episodes/patient-year in the liraglutide 1.2 mg and 1.8 mg and sitagliptin groups, respectively. One case of nonacute pancreatitis, possibly treatment-related, was reported in a patient treated with liraglutide 1.8 mg.

Case Study

The PCP concludes that although the weight neutral effect and low incidence of hypoglycemia associated with the DPP-4 inhibitors would be beneficial for KB, the magnitude of glucose lowering is likely to be less than needed to achieve A1C <7.0%. The PCP begins a discussion of the attributes of the GLP-1R agonists, particularly the weight loss effect. Upon mentioning that the GLP-1R agonists require self-injection, KB interrupts and states that she doesn't want to put up with the hassle of self-injecting. Instead, she would rather take a tablet once a day. Although the PCP agrees to initiate glimepiride 4 mg QD, she recognizes that an injectable glucose-lowering agent may be needed soon, so she discusses the devices involved and shows KB how they are used.

At 6-week follow-up, the A1C has declined to 7.9%, but KB's body weight has risen to 93.4 kg (increase of 1.1 kg from last visit). She experienced 1 transient episode of lightheadedness and nausea, but she did not measure her blood glucose. KB expresses frustration that she has gained more weight and complains that she is finding it increasingly difficult to remain motivated about taking her medications. The PCP reminds KB that a GLP-1R agonist would likely provide the A1C reduction needed and she would very likely lose weight. More receptive than during the previous visit, KB asks to be shown the devices again and how they are used. KB's insurance company is contacted and verifies that treatment with a GLP-1R agonist would be covered subject to the deductible and copay. To individualize therapy to best meet KB's needs and circumstances, the PCP considers the differences among the GLP-1R agonists.

Comparison of the GLP-1R Agonists

Beyond the differences described in **TABLE 2**, the frequency of administration is different for each of the 3 GLP-1R agonists. Exenatide is available in 2 different formulations, 1 for administration BID and the other QW, while liraglutide is administered QD. Whereas exenatide QW and liraglutide can be taken without regard to meals, exenatide BID must be taken 60 minutes prior to mealtime, typically breakfast and dinner. Exenatide BID is available as a prefilled pen with a 29, 30, or 31 gauge needle, and liraglutide as a prefilled pen with a 30 or 32 gauge needle. Exenatide QW comes as a kit that requires using a diluent (supplied) to prepare a suspension of exenatide. Using the 23 gauge needle provided, exenatide QW must be administered immediately after preparing the suspension. Additional differences among the GLP-1R agonists have been identified in prospective, randomized, head-to-head clinical trials.

Head-to-Head Clinical Trials of GLP-1R Agonists

Exenatide BID vs Exenatide QW

Two-hundred-ninety-five patients with T2DM who were drug-naïve or taking 1 or more oral glucose-lowering agents were randomized to exenatide 10 mcg BID or exenatide 2 mg QW.[15] Both groups received exenatide 5 mcg BID for 3 days; patients in the exenatide BID group received an additional 28 days of 5 mcg BID before uptitration to 10 mcg BID. Mean baseline values were A1C 8.3%, FPG 162 mg/dL, weight 102 kg, and diabetes duration

6.7 years. At 30 weeks, reduction in the A1C level was greater with exenatide QW than exenatide BID (–1.9% vs –1.5%; $P = .0023$). Significantly more patients receiving exenatide QW achieved A1C ≤7.0% (77% vs 61%; $P = .0039$). Similarly, greater reductions in the FPG (–41 mg/dL vs –25 mg/dL, $P < .0001$) and 2-hour PPG (–124 mg/dL vs –95 mg/dL, $P = .0124$) levels were observed with exenatide QW than exenatide BID, respectively. Body weight decreased progressively in both groups, with a reduction of 3.6 to 3.7 kg at 30 weeks. In patients not receiving sulfonylurea therapy, 1 episode of minor hypoglycemia occurred in a patient treated with exenatide QW.

A 22-week open-label extension showed sustained improvements in glycemic control and body weight with exenatide QW.[14] Patients switched from exenatide BID to exenatide QW experienced further improvements in A1C and FPG levels such that both groups exhibited the same A1C reduction and mean A1C (6.6%) at week 52. Reductions in body weight were –4.1 and –4.5 kg in the exenatide QW and exenatide BID/QW groups, respectively.

Exenatide BID vs Liraglutide

Adults with T2DM inadequately controlled with metformin, sulfonylurea, or both were randomized to exenatide 10 mcg BID or liraglutide 1.8 mg once daily for 26 weeks in an open-label study; exenatide BID was uptitrated over 4 weeks and liraglutide over 2 weeks.[10] Liraglutide reduced the mean A1C significantly more than exenatide BID (–1.12% vs –0.79%; $P < .0001$). More patients in the liraglutide group achieved an A1C <7.0% (54% vs 43%; $P = .0015$). The reduction in FPG was significantly greater with liraglutide than exenatide BID (–29 mg/dL vs –11 mg/dL; $P < .0001$). Exenatide BID reduced PPG excursions after breakfast and dinner more than liraglutide; improvement in PPG excursions after lunch were similar. Weight loss was similar in both groups (–2.87 kg with exenatide BID vs –3.24 kg with liraglutide 1.8 mg). Improvements in fasting insulin, pancreatic β-cell function, triglyceride, very LDL-C, and free fatty acids were significantly greater with liraglutide ($P < .05$), whereas improvements in fasting glucagon and systolic and diastolic blood pressure were similar in both groups. In patients taking metformin, minor hypoglycemia occurred in 11% and 6% of patients treated with exenatide BID and liraglutide, respectively. Nausea and vomiting occurred slightly less frequently with liraglutide, with nausea persisting at 26 weeks in 3% of liraglutide patients and 9% of exenatide patients.

A 14-week open-label extension showed sustained improvements in patients continuing liraglutide, with further significant decreases in body weight (0.4 kg) and systolic BP (2.2 mm Hg).[50] Minor hypoglycemia occurred at a low rate (0.74 episodes/patient-year). In patients switched from exenatide BID to liraglutide, further and significant reductions were observed in A1C (0.32%), FPG (16 mg/dL), body weight (0.9kg), and systolic BP (3.8 mm Hg). The rate of minor hypoglycemia was reduced by 50% compared with the first 26 weeks to a rate of 1.30 episodes/patient-year over the 14 weeks.

Exenatide QW vs Liraglutide

Adults with T2DM inadequately controlled with single or 2-drug combination oral therapy were randomized to exenatide 2 mg QW or liraglutide 1.8 mg QD (uptitration over 2 weeks).[51] After 26 weeks, reductions in the A1C (–1.48% vs –1.28%; $P = .02$) and FPG (–38 mg/dL vs –32 mg/dL; $P = .02$) were significantly greater in the liraglutide group compared with the exenatide QW group, respectively. More patients in the liraglutide group achieved A1C <7.0% (60% vs 53%; $P = .0011$). Patients treated with liraglutide lost more body weight than patients treated with exenatide QW regardless of baseline BMI (–3.57 kg vs –2.68 kg). Systolic BP decreased –3.45 mm Hg in the liraglutide group and –2.48 mm Hg in the exenatide QW group. Similar but small reductions in the lipid profile were observed in both groups. Gastrointestinal adverse events (nausea, vomiting, diarrhea) were the most common, with a greater frequency in the liraglutide group. Injection site adverse events (nodule, pruritus, erythema) were more common with exenatide QW. In those not taking concomitant sulfonylurea, minor hypoglycemia episodes occurred in 3% of patients treated with liraglutide and 4% treated with exenatide QW.

Case Study

Feeling less anxious about injecting a GLP-1R agonist, following the discussion and demonstration by her PCP and encouraged by the prospect of losing weight, KB agrees to begin treatment with a GLP-1R agonist. Knowing that KB is likely to experience nausea and/or vomiting associated with a GLP-1R agonist, the PCP provides KB with a list of the most common adverse events associated with GLP-1R agonist therapy and their management. They discuss strategies to improve adherence, as well.

Strategies to Reduce the Incidence and Severity of Nausea and Vomiting

The nausea that occurs with GLP-1R agonist therapy is generally mild in severity, causing drug discontinuation in fewer than 2% of patients.[8,16] The severity of nausea generally peaks within 8 weeks of starting exenatide BID, 4 to 8 weeks of starting liraglutide, and shortly after initiating exenatide QW.[8,16,52,53] Resolution of nausea occurs in about 90% of patients within 28 weeks of initiating exenatide BID and 8 weeks with liraglutide. In patients treated with exenatide QW, nausea resolves in nearly all patients within 10 weeks.[8,16,52,53]

Initiating therapy using a dose escalation strategy is recommended for exenatide BID and liraglutide, but is not needed for exenatide QW. For exenatide BID, initiation should begin with 5 mcg BID. Based on clinical response, the dose can be increased to 10 mcg BID after 4 weeks.[35] Liraglutide is initiated at a dose of 0.6 mg QD for 1 week, increasing to 1.2 mg QD after 1 week. If acceptable glycemic control is not achieved, the dose of liraglutide can be increased to 1.8 mg QD.[37] Additional strategies to reduce the incidence and severity of nausea include[54-56]

- Stop eating when feeling full
- Eat small meals
- Avoid high-fat meals
- Lengthen time period during which dose escalation is achieved
- Temporarily reduce the dose
- Take exenatide BID closer to mealtime than 60 minutes
- Switch to a different GLP-1R agonist

Premedication with oral antiemetic therapy is a further option. A reduction in the incidence of nausea and vomiting has been observed with single oral doses of the combination of metoclopramide 10 mg and ondansetron 8 mg administered 30 minutes prior to therapy.[57]

Strategies to Improve Adherence

Numerous strategies have been demonstrated to improve medication adherence. These include developing and maintaining a positive, collaborative relationship with each patient and providing ongoing support by a multidisciplinary care team, with frequent reinforcement and reminders. The patient should receive ongoing education about their disease, risks and benefits of treatment, goals and duration of treatment, and nonpharmacologic and pharmacologic treatment options, as well as self-management training.[58] Because many patients with T2DM feel overwhelmed with the self-management needed, keeping the treatment plan as simple as possible is important. As illustrated in the case study, frequent treatment-related adverse events should be discussed with patients and management strategies provided (preferably in writing).

Discussing the benefits of treatment with each medication is also important, as these can serve to motivate patients. With the GLP-1R agonists, for example, the ability to promote weight loss and the low risk of hypoglycemia have been shown to contribute to patient satisfaction.[59-63] Developing and periodically reevaluating the treatment plan with the patient is critical to ensure that the plan best meets his or her individual situation, including life expectancy, affordability, and social support.

Many diabetes-related tools for providers and patients are available as smartphone applications. A list of these applications is available from the American Diabetes Association (http://forecast.diabetes.org/apps-jan2013); a review of 10 of these applications was recently published.[64]

Conclusion

Type 2 diabetes mellitus is a complex disorder with multiple pathologic mechanisms, 1 of which is decreased secretion of GLP-1 in response to meals. The GLP-1R agonists and DPP-4 inhibitors act via different mechanisms on the incretin system, resulting in clinically important differences in glycemic and non-glycemic effects. The major differences include greater A1C reduction, as well as reduced caloric intake and weight loss, with the GLP-1R agonists. While the GLP-1R agonists require subcutaneous administration and frequently cause nausea, various strategies can be employed to individualize therapy and improve treatment adherence. ■

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