CLINICAL REVIEW

An Evidence-Based and Practical Approach to Using Bydureon™ in Patients With Type 2 Diabetes

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Glucagon-like peptide (GLP)-1 agonists are one of the newer classes of medications for use in type 2 diabetes. There are currently three GLP-1 agonists on the market: exenatide twice daily, liraglutide, and exenatide extended release (ER). Exenatide ER is a new weekly formulation of exenatide. Exenatide ER reduces glycosylated hemoglobin by 1.6%, with fewer gastrointestinal side effects compared with twice-daily exenatide. Like other GLP-1 agonists, exenatide ER can be used in combination with metformin, sulfonylureas, or thiazolidinediones. Patients should be assessed for risk of pancreatitis and renal impairment. Education about proper administration technique is vital with the novel delivery system. Prescribers may also consider the use of exenatide ER to improve medication adherence in patients who have successfully tolerated exenatide twice daily or use in patients who have gastrointestinal side effects with exenatide twice daily. Exenatide is a reasonable option that can be added to the regimen of a patient with type 2 diabetes. (J Am Board Fam Med 2013;26:203–210.)

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It is estimated that nearly 26 million Americans have diabetes mellitus, with type 2 diabetes mellitus accounting for nearly 90% of all diabetes cases.[1] In a recent study, less than half of patients with type 2 diabetes who started taking insulin as monotherapy or in combination with other medications for diabetes achieved an glycosylated hemoglobin (A1c) level of <7% within 9 months.[2] Patients achieving an A1c <7% were more likely to have started the study with lower A1c levels.[2] Achieving glycemic goals can be challenging, which highlights the need for a multifaceted approach that includes interprofessional care.

Type 2 diabetes is characterized by a deficiency in insulin production, peripheral insulin resistance, impaired regulation of hepatic glucose production, and an eventual decline in β-cell function. In addition to lifestyle changes, metformin is considered first-line therapy for the treatment of type 2 diabetes, but many patients will require multiple medications to achieve adequate glycemic control.[3,4]

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide are regulatory peptides called incretins, which are secreted by the intestines in response to food intake. GLP-1 helps maintain glucose homeostasis by enhancing glucose-dependent insulin secretion, suppressing glucagon release, slowing gastric emptying, decreasing food intake, and increasing satiety. Physiologic GLP-1 has a very short half-life and is degraded by dipeptidyl peptidase-4 (DPP-4) in 1.5 to 2 minutes.[5] Several medications affect this pathway. Exenatide and liraglutide are GLP-1 receptor agonists that mimic the physiologic action of endogenous GLP-1 (Table 1).

DPP-4 inhibitors also are a class of medications that affect the incretin system (Table 1). Patients with diabetes often have a diminished GLP-1 response that correlates with insulin resistance. By blocking the enzyme that breaks down GLP-1 and other incretins, endogenous GLP-1 has a more pronounced effect. Although DPP-4 inhibitors

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Table 1. Food and Drug Administration–Approved Incretins and Clinical Effects as Monotherapy[6–11]

	GLP-1 Agonists or Analogs			DPP-4 Inhibitors		
	Exenatide ER (Bydureon)	Exenatide (Byetta)	Liraglutide (Victoza)	Sitagliptin (Januvia)	Saxagliptin (Onglyza)	Linagliptin (Tradjenta)
Route	SQ	SQ	SQ	Oral	Oral	Oral
Dosing frequency	Once a week	Twice a day	Daily	Daily	Daily	Daily
Change in A1c, %	−1.6	−0.9	−1.1	−0.5	−0.5	−0.4
Change in weight, kg	−2.0	−2.5	−1.9	−1.5	−1.1	−1.0
Hypoglycemia	±	±	±	—	—	—
Adverse GI effects	+	+ +	+ +	—	—	—
Approximate monthly cost of therapy ($),[12]	370	360	520	260	260	280

ER, extended release; GLP, glucagon-like peptide; DPP, dipeptidyl peptidase; GI, gastrointestinal; SQ, subcutaneously.

have the advantage of being oral agents, they do not cause weight loss and have a modest glucose-lowering effect.[5]

GLP-1 agonists have a longer half-life than endogenous GLP-1 because of structural differences and other chemical modifications. Exenatide extended-release (exenatide ER; Bydureon, Amylin Pharmaceuticals, Inc., San Diego, CA) uses a proprietary controlled release formulation (Medisorb microspheres) to provide a continuous amount of exenatide over a 7-day period.[13,14] All GLP-1 agonists have been shown to improve glycemic control and promote weight loss, but they can cause significant nausea and gastrointestinal (GI) adverse effects as they slow gastric emptying.

The U.S. Food and Drug Administration originally approved twice-daily exenatide in April 2005. Exenatide ER was approved in January 2012 as monotherapy or in combination with other medications for the treatment of type 2 diabetes. Diabetes Therapy Utilization: Researching Changes in HBA1C, Weight, and Other Factors Through Intervention with Exenatide Once Weekly (DURATION) is a series of clinical trials designed to compare exenatide ER with other medications to treat type 2 diabetes that are already on the market. These data and results from other trials, as well as some of the implications to clinical practice, are discussed herein.

Clinical Effects of Exenatide ER

Compared with exenatide twice daily, exenatide ER has demonstrated improvements in glycemic control, cardiovascular parameters, weight, and nausea. In DURATION-1, patients with a baseline A1c of 8.3% who were taking metformin, a sulfonylurea, thiazolidinedione, or any combination of 2 of these agents received exenatide ER or exenatide twice daily for 30 weeks.[15] At the conclusion of the trial, subjects receiving exenatide ER experienced a significantly greater reduction in A1c than those taking exenatide twice daily (−1.9% and −1.5% respectively; $P = .0023$). Weight loss was similar between both groups, but the patients receiving exenatide ER experienced less nausea. Similar results were noted in the DURATION-5, where more than 250 patients (already taking metformin, sulfonylurea, thiazolidinedione, or a combination of these medications) with a baseline A1c of 8.4% were randomized to exenatide ER or exenatide twice daily and followed for 24 weeks. Subjects taking exenatide ER experienced a 1.6% lowering of A1c ($P < .0001$) and a 35-mg/dL decrease in fasting plasma glucose ($P = .0008$) compared with 0.9% and 12 mg/dL, respectively, for exenatide twice daily. Subjects taking exenatide ER experienced a small reduction in systolic blood pressure (BP) (−2.9 mm Hg) but a slight increase in diastolic BP (0.2 mm Hg) compared with exenatide twice daily (−1.2 mm Hg systolic BP; −0.1 mm Hg diastolic BP). Small but statistically significant improvements were reported in total cholesterol and low-density lipoprotein levels ($P < .01$). Subjects randomized to exenatide ER experienced a reduction in weight (−2.3 kg; $P = .01$) compared with those taking exenatide twice daily (1.4 kg).[16]

Exenatide ER Compared With Metformin

Although numerous controlled clinical trials have demonstrated the efficacy of exenatide twice daily and exenatide ER compared with or in combination with other diabetes medications, few controlled trials have evaluated the efficacy of exenatide ER in

combination with metformin. In a small, randomized, placebo-controlled, phase 2 trial, 2 doses of exenatide ER were studied to assess glucose control and body weight in 45 subjects with type 2 diabetes. All subjects who had received exenatide in previous trials were excluded. Treatment with the same dose of metformin throughout the study period was permitted. Exenatide ER was administered subcutaneously once weekly for 15 weeks, followed by a 12-week safety observation period. Compared with a baseline A1c of 8.5%, at 15 weeks both doses resulted in a statistically significant ($P < .05$) change in A1c of −1.7%. Reduction of A1c was observed at week 3, the first data point measurement demonstrating a relatively rapid glycemic response. Approximately 80% of subjects receiving the 2-mg dosage achieved A1c of <7% by the end of the study. Exenatide ER also improved fasting plasma glucose and postprandial plasma glucose concentrations. A progressive reduction in body weight was observed (−3.8 kg, or 3.5% reduction of total body weight), whereas weight remained unchanged in the placebo group. GI adverse events were the most commonly reported, with the highest incidence of mild nausea in the group receiving the 2-mg dosage (27%) compared with placebo (15%). Adverse events in the groups taking exenatide ER did not account for any study withdrawals.[17]

Exenatide ER Compared With Insulin

DURATION-3 compared exenatide ER with insulin glargine that was titrated based on fasting plasma glucose for 26 weeks in patients with a baseline A1c of 8.3% who were taking maximum doses of metformin or a combination of metformin and a sulfonylurea. Differences were noted in A1c, weight, and systolic BP. Exenatide ER showed a change in A1c of −1.5% compared with −1.3% in the subjects treated with insulin glargine. Those receiving exenatide ER experienced a weight change of −2.6 kg, whereas subjects taking insulin glargine experienced a weight change of −1.4 kg. Both groups showed a modest change in systolic BP: −3 mm Hg for exenatide ER and −1 mm Hg for insulin glargine.[18]

Exenatide ER Compared With Other Injectable Diabetes Medications

Exenatide ER offers slightly less A1c lowering than liraglutide but has a lower rate of side effects. A comparison of liraglutide 1.8 mg daily and exenatide ER showed that patients receiving exenatide ER experienced an A1c change of −1.3% compared with −1.5% for liraglutide at 6 months. Patients experienced more GI adverse effects with liraglutide compared with exenatide ER: nausea, 20.4% versus 9.4%; diarrhea, 13.1% versus 6.1%; and vomiting, 10.7% versus 3.7%, respectively.[19]

Exenatide ER in Combination With Oral Diabetes Medications

Exenatide ER has been used in combination with many oral diabetes medications and has been shown to improve glycemic control. In a 26-week trial (DURATION-2), exenatide ER, pioglitazone, or sitagliptin were added to ongoing treatment with metformin. Patients treated with exenatide ER achieved a mean A1c change of −1.5% versus −0.9% for sitagliptin and −1.2% for pioglitazone.[20] Similar results were obtained in a separate 26-week, 4-arm comparator study of exenatide ER versus sitagliptin, metformin, or pioglitazone in patients with an uncontrolled diet and only exercise. Patients receiving exenatide ER achieved a mean A1c change of −1.5% versus −1.2% for sitagliptin.[21]

Safety Considerations With Exenatide ER

Exenatide ER generally has been shown to be well tolerated; nausea, hypoglycemia, and injection site reactions are the most commonly reported adverse effects. GI adverse effects are the most commonly reported side effects with exenatide ER. Mild to moderate nausea was the most common issue, but the incidence was lower with exenatide ER (7% to 14%) than it was with exenatide twice daily (35%), suggesting that a gradual increase in exenatide concentrations in plasma may reduce the incidence of GI side effects.[15,16] The incidence of nausea with exenatide ER decreases with time.

Hypoglycemia

Minor hypoglycemia occurred in 8% of patients taking exenatide ER when it was used as monotherapy compared with 26% of patients using insulin glargine.[18] When a sulfonylurea was combined with exenatide ER or exenatide twice daily, 9% of patients reported mild hypoglycemia. When initiating exenatide ER in patients taking sulfonyl-

Table 2. Patient Selection Considerations[6,23]

Considerations	Comments
Objective criteria	
Diagnosis of type 2 diabetes mellitus	FDA indication
Triglycerides <500 mg/dL	Reduce risk for pancreatitis
No history of or current issues with alcoholism	Reduce risk for pancreatitis
Amylase WNL	Reduce risk for pancreatitis
Lipase WNL	Reduce risk for pancreatitis
No history of current or recurrent pancreatitis	Reduce risk for pancreatitis
No history of current or recurrent gallstones	Reduce risk for pancreatitis
Normal or mild renal impairment (CrCL >60 mL/min)	Caution with CrCL 30–60 mL/min; avoid in those with CrCL <30 mL/min or ESRD
Normal hepatic function	Caution in acute or chronic hepatic impairment; effects are unknown
Others	
Concurrently taking a sulfonylurea agent	Halve the sulfonylurea agent dose to reduce risk of hypoglycemia; educate patient on signs/symptoms of hypoglycemia and appropriate treatment
Dexterity	Drug requires self-reconstitution and injection
Digit manipulation issues: arthritis, rheumatoid arthritis	Drug requires self-reconstitution and injection
Adherence	Remembering weekly drug administration
Tolerability	Consider using in patients who have tolerated exenatide twice daily

CrCL, creatinine clearance; FDA, U.S. Food and Drug Administration; ESRD, end-stage renal disease; WNL, within normal limits.

ureas, the dose of the sulfonylurea should be lowered to prevent hypoglycemia.[6]

Injection Site Reactions

Injection site reactions are observed more frequently in patients treated with exenatide ER (17.1%) than in patients treated with exenatide twice daily (12.7%) and titrated insulin glargine (1.8%).[9] These reactions include bruising, erythema, hemorrhage, induration, pain, skin nodules, and pruritus at the injection site. Mild to moderate injection site pruritus occurred after switching from exenatide twice daily to exenatide ER in 4.6% of patients, of whom 83% did not have pruritus when taking exenatide twice daily.[1,5] The incidence of injection site reactions with exenatide ER decreases with time and with continued use. Exenatide ER may cause small, asymptomatic, subcutaneous injection site nodules, which are consistent with known properties of the microspheres used in the product. These nodules often resolve without intervention.[6]

Anti-Exenatide Antibodies

Anti-exenatide antibodies have been observed in patients taking exenatide ER and exenatide twice daily.[16,18] Exenatide ER is associated with higher levels of anti-exenatide antibodies than exenatide twice daily. In 6% of patients treated with exenatide ER, antibody formation has been associated with an attenuated glycemic response. In addition, injection-site reactions related to exenatide ER were observed more often in antibody-positive patients (14.2%) than antibody-negative patients (3.1%), and patients with higher titer antibodies have a higher incidence of these reactions.[6,22]

Pancreatitis

Acute pancreatitis has been observed in patients treated with exenatide ER, with full resolution of the symptoms after discontinuation of the agent. Although likely rare, there is a concern that if pancreatitis occurs, effects of exenatide ER could persist for many weeks because of its long duration of action.[15] After initiating exenatide ER, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, exenatide ER should be discontinued immediately and appropriate management initiated. If pancreatitis is confirmed, exenatide ER should not be restarted. Other diabetes therapeutic agents besides exenatide ER should be considered for patients with a history of pancreatitis.[6,7] Patient selection parameters for initiating exenatide ER are outlined in Table 2.

Thyroid Tumors

Exenatide ER carries a boxed warning that it causes an increased incidence in thyroid C-cell tumors in rats.[6] While there have been no reports of thyroid neoplasms with exenatide ER in humans, exenatide ER should not be used in patients with a medical or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.[6] When obtaining exenatide ER from their pharmacy, patients will be provided with a mandatory medication guide that discusses the risk of possible thyroid tumors, cancers, and pancreatitis with this agent.

Drug Interactions

Exenatide slows gastric emptying. As a result, exenatide has the potential to reduce the rate of absorption of orally administered drugs. Clinicians should be aware of this potential interaction, especially when drugs with narrow therapeutic margins are concomitantly prescribed with exenatide ER.[6]

While exenatide ER has not been studied with warfarin, exenatide did not have a significant effect on international normalized ratio (INR). Reports after marketing have revealed an increased INR with exenatide and concomitant use of warfarin, sometimes associated with bleeding. When initiating exenatide ER in a patient who is also taking warfarin, INR should be monitored more frequently until a stable INR has been achieved.[6]

Patient Dosing and Administration Education[6,23]

Dose

Exenatide ER is supplied in cartons of 4 single-dose trays that a patient uses once every 7 days. The dose of exenatide ER is 2 mg injected subcutaneously once a week, without regard to food. It can be injected into the abdomen, thigh, or upper arm. If a patient misses a dose of exenatide ER, it should be injected as soon as the patient remembers. Two doses should not be injected within 3 days.[7]

Renal Impairment

Exenatide ER should not be used in patients with a creatinine clearance of <30 mL/min or end-stage renal disease because it is primarily eliminated through the kidneys. In addition, caution should be used when using exenatide ER in patients with moderate renal impairment (creatine clearance 30–50 mL/min).

Figure 1. Steps for mixing exenatide extended release.

1. Remove the vial connector from its packaging
2. Connect the vial and vial connector
3. Connect the syringe to the vial using the vial connector
4. Inject the diluent from the syringe into the vial
5. Shake the mixture vigorously until no clumps are visible (will be cloudy)
6. Remove the vial from the syringe
7. Attach a needle to the syringe
8. Inject the medication solution

Hepatic Impairment

Pharmacokinetic studies have not been conducted with exenatide ER in patients with acute or chronic hepatic impairment. However, because exenatide ER is cleared mainly by the kidneys, it is not expected that mild or moderate hepatic impairment would affect the pharmacokinetics of exenatide ER.

Severe GI Disease

Exenatide ER can delay gastric emptying and is associated with nausea, vomiting, and diarrhea. As such, it is not recommended for patients with severe GI disease.

Geriatrics

The pharmacokinetics of exenatide ER do not seem to be altered with increasing age. However, normal renal function should be confirmed in geriatric patients before initiating this agent.

Pregnancy/Lactation

Exenatide ER is contraindicated in pregnant or lactating women.

Mixing

Each dose of medication is packaged with the necessary components for self-administration. These components include a vial containing the medication powder, a vial connector, a syringe with diluent, and 2 needles. The medication must be mixed in a multistep process before injection (Figure 1). Exenatide ER must be injected at a 90 degree angle immediately after mixing. A step-by-step instructional video about exenatide ER administration is available to patients.[24] Exenatide ER packaging also includes patient instruction materials explaining self-administration of the medication. Up to 15%

of patients fail to complete at least one essential step for self-administration.[25]

Switching from Exenatide Twice Daily

Exenatide twice daily contains the same active drug as exenatide ER. As such, exenatide twice daily should be stopped 24 hours before initiating exenatide ER. For example, a patient taking exenatide twice daily who will be starting exenatide ER on a Sunday morning should inject their last dose of exenatide twice daily on Saturday morning.[6] When switching from exenatide twice daily, patients may experience an initial slight increase in blood glucose levels (~13 mg/dL) for up to 2 weeks. Most patients should notice a decrease in fasting blood glucose levels after 2 weeks.[26]

Injection Differences (Needle Length and Size)

The needles included with the exenatide weekly packaging are 23-gauge, 5/16-inch needles, which are larger than insulin needles. The needles are developed specifically for exenatide ER and cannot be substituted with other commercially available needles.[6] Insulin often is injected with needles that are 25 gauge or smaller. The diluent-medication suspension may clog the needle and patients must change the needle for successful administration.[23] No data are available on how frequently the second needle is needed.

Injection Site Issues

Itching at the injection site is a common side effect of exenatide ER. Some patients report the formation of nodules that may range in size from 0.5 to 0.75 cm. These usually resolve without intervention.[14]

Patient Education

Patients can be advised that they should observe an improvement in their fasting blood glucose within 2 weeks. Exenatide ER provides progressive weight reduction, and weight loss of up to 2 kg may be observed after 4 to 5 months with continued use of exenatide ER.

Patients should be aware that although nausea may occur after exenatide administration, it usually diminishes with continued use, and it is less frequently seen than with exenatide twice daily. Nausea may be relieved by sucking on hard sugar-free candy. Strategies to prevent nausea include eating smaller portions during meals, increasing fluid intake, and avoiding fried, fatty, or spicy foods.

Mild or moderate itching or pain at the injection site may occur. While a cold/hot pack or a topical glucocorticosteroid cream, such as hydrocortisone 0.5% to 1% cream, may be applied to the injection site if symptoms are troublesome, clinical studies did not specifically evaluate the efficacy of such agents in alleviating itching or pain. Symptoms usually resolve a few days after exenatide ER administration.

Patients should be advised that exenatide may cause hypoglycemia, especially if they are taking a sulfonylurea or a meglitinide, and should be advised to carry a source that delivers glucose quickly, such as 3 to 4 glucose tablets, with them at all times. Symptoms of pancreatitis should be reviewed with the patient before initiating exenatide ER and patients advised to discontinue its use and call their physician immediately if symptoms occur.

Exenatide ER should be stored in the refrigerator. However, if a patient is traveling they may be advised that exenatide ER is stable at room temperature at <77°F for up to 4 weeks.

If a dose is missed, exenatide ER should be administered as soon as it is remembered, unless it is within 72 hours of the next scheduled dose. Exenatide ER should not be readministered until at least 72 hours have passed after the previous injection.

Storage

Exenatide ER should be stored in the refrigerator (36–46°F or 2–8°C) but is stable at room temperature (68–77°F or 20–25°C) for up to 4 weeks. Exenatide ER should not be frozen.[23]

Conclusions

Exenatide ER is an effective medication with clinical efficacy and side effect profile improved over twice-daily exenatide, with the additional benefit of weekly administration (level 1 evidence, Strength of Recommendation Taxonomy [SORT] A). Clinical trials have demonstrated that exenatide ER can be used in addition to frequently used oral diabetes medications and has been compared with twice-daily exenatide, insulin glargine, and liraglutide. Patients should be carefully screened for comorbid conditions that may increase the risk of adverse drug reactions (level 3 evidence, SORT C). When

patients are switched from exenatide twice daily to exenatide ER, they may experience a transient deterioration in their glycemic control, which improves 2 weeks after initiating exenatide ER.

Careful instruction should also be provided to ensure proper administration technique (level 3 evidence, SORT C). Prescribers may also consider use of exenatide ER in patients who have successfully tolerated exenatide twice daily to minimize adverse effects because of the extended duration of exenatide ER. Clinicians can consider adding exenatide ER to the arsenal of existing medications to help improve glycemic control of patients with type 2 diabetes. With the increasing focus on patient-centered care and individualized goals,[27] exenatide weekly is a well tolerated option to help improve A1c, reduce weight, and avoid hypoglycemia.

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