GLP-1 Agonists Therapy in Individuals with Type 2 Diabetes Mellitus: A Review of Safety and Tolerability

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“GLP-1 Agonists Therapy in Individuals with Type 2 Diabetes Mellitus: A Review of Safety and Tolerability” is one in a series of continuing education articles authored and generously contributed to the Missouri Pharmacy Association by the Indiana Pharmacists Alliance.

Learning Objectives:
1. Explain the role of the incretin system in the development of diabetes and discuss the place in therapy for GLP-1 agonists.
2. Compare and contrast the adverse effects and safety profiles of the two FDA-approved GLP-1 agonists, exenatide and liraglutide.
3. Discuss the appropriate use and recommendations of GLP-1 agonists in terms of their safety profile.
4. Discuss the patient education that should be provided upon prescribing and/or dispensing exenatidine and liraglutide based on the REMS system.
5. Discuss the proposed mechanism and risk factors the GLP-1 agonist safety concerns.

Recent medication advances in the treatment of type 2 diabetes mellitus (T2DM) have evolved around the incretin system, specifically with a focus on the glucagon-like peptide-1 (GLP-1) hormone. Research has shown that GLP-1 hormones and receptors play an integral and multifactorial role in the homeostasis of glucose via pancreatic and extrapancreatic mechanisms.1,2,3 GLP-1 hormones exert their effects by binding to structurally distinct receptors which are located in the α- and β-pancreatic islet cells, in addition to the kidneys, lungs, heart, brain, and the nervous system.1,2 Through a constellation of activities, such as stimulating insulin synthesis and release, decreasing hepatic gluconeogenesis, increasing insulin sensitivity and glucose uptake, decreasing glucagon secretion, increasing satiety and decreasing gastric emptying, the native GLP-1 hormones aid in regulating both post-prandial and fasting glucose concentrations.1,2,3 However, shortly after release from the distal L cells of the gastrointestinal tract in a nutrient-dependent manner, biologically active native GLP-1 hormones are rapidly cleaved at the N-terminal into an inactive form by the dipeptidyl peptidase 4 (DPP4) enzyme.1,2,3 This cleavage of the biologically active GLP-1, results in a half-life of approximately 1.5 minutes and limits the glucose-lowering action of GLP-1.1,2 In addition to degradation by the DPP4 enzyme, the physiological activity of native GLP-1 is further limited by its’ rapid clearance from circulation via the kidney.1 Furthermore, studies have shown the incretin effect, which is the phenomenon that the increase in insulin secretion after oral ingestion of glucose is greater than that seen with IV glucose administration, particularly in postprandial states, is blunted in individuals with T2DM, impeding the achievement of euglycemia, further supporting their use as a viable treatment option.1,3,4

Clinical investigations found that intravenous administration of recombinant human GLP-1 resulted in increased insulin secretion, decreased glucagon release, and subsequently lowered fasting and postprandial levels in individuals with T2DM. While these findings did demonstrate the positive therapeutic outcomes that are associated with restoring and enhancing the incretin action of GLP-1 hormones, clinical use was limited by a short-half life and inconvenient route of administration.1,4 In addition to the aforementioned glucose lowering effects, findings suggest GLP-1 hormones have a positive impact on B-cell proliferation and reduces apoptosis.2 Additionally, although further studies are needed, it appears that both exenatide and liraglutide exhibit the ability to preserve beta cell function and improve cardiac function, including but not limited to improving blood pressure, lipid concentrations, myocardial function, and cardiac output, specifically by reducing left ventricular end diastolic pressure, all of which are
possible concomitant medical conditions in patients with T2DM.\textsuperscript{2,4} Thus, the development of chemically enhanced GLP-1 receptor (GLP-1R) agonists with superior pharmacokinetic profiles and resistance to DPP4 enzyme degradation has become the pharmacological target for the treatment of T2DM.\textsuperscript{2,4} To date, there are two chemically modified GLP-1R agonists available in the United States, exenatide and liraglutide.

Exenatide (Byetta\textsuperscript{\textregistered}, Amylin Pharmaceuticals Inc, San Diego, California, and Eli Lilly, Indianapolis, Indiana), a synthetically modulated version of GLP-1 made from the venom of the Gila-monster, was Federal Drug Administration (FDA) approved in April 2005 for monotherapy or combination therapy with metformin, a thiazolidinedione (TZD), or a sulfonylurea to improve glycemic control in patients with T2DM.\textsuperscript{5} In October 2011, exenatide received FDA approval for its use in combination with glargine insulin.\textsuperscript{5} Exenatide shares 53\% homology with native human GLP-1 hormones.\textsuperscript{2,3,5} Liraglutide (Victoza\textsuperscript{\textregistered}, Novo Nordisk Inc, Princeton, New Jersey), on the other hand, is designed by recombinant DNA technology, shares 97\% homology to native human GLP-1 hormones, and was FDA-approved in January 2010 as adjunct to diet and exercise to improve glycemic control in patients with T2DM.\textsuperscript{2,3,6} It is important to mention that unlike exenatide, the manufacturer does not recommend liraglutide as monotherapy.\textsuperscript{5} Exenatide and liraglutide, which are available via subcutaneous administration, mimic all of the glucose lowering actions of native human GLP-1 hormones.\textsuperscript{1-4} Specific dosing information can be found in table 1.

Table 1: GLP-1 Prescribing Information

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>Adult Dosing</th>
<th>Dosing in Renal Impairment</th>
</tr>
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<tbody>
<tr>
<td>Exenatide (Byetta\textsuperscript{\textregistered})\textsuperscript{\textsuperscript{\textcopyright}} Available in pre-measured pens of 5- and 10 mcg</td>
<td>5 mcg twice daily for 30 days then, if tolerated, titrate to 10 mcg twice daily thereafter. Inject subcutaneously within 60 minutes before breakfast and dinner (separate doses by at least 6 hours).</td>
<td>Severe renal impairment (creatinine clearance &lt;30 ml/min) or end-stage renal disease: Avoid therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate renal impairment (creatinine clearance 30 to 50 ml/min): Apply caution when initiating or increasing therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal renal function: Monitor patients carefully for the development of kidney dysfunction, and evaluate the continued need suspect exenatide induced kidney dysfunction</td>
</tr>
<tr>
<td>Liraglutide (Victoza\textsuperscript{\textregistered})\textsuperscript{\textsuperscript{\textcopyright}} Available in pre-measured pen with a dose titration feature</td>
<td>0.6 mg daily for 7 seven days, then increase to 1.2 mg or 1.8 mg Inject subcutaneously daily regardless of timing of meals. Note: 0.6 mg daily is ineffective for glycemic control</td>
<td>No renal adjustment needed. Exercise caution when initiating or increasing therapy.</td>
</tr>
</tbody>
</table>

According to the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Glycemic Control Algorithm for individuals with T2DM published in 2009, GLP-1R agonists are indicated as an option for 1\textsuperscript{st} line therapy, particularly in individuals with elevated post-prandial glucose concentrations.\textsuperscript{7} Furthermore, it recommends GLP-1R agonists as an option for the second component of dual therapy, in combination with metformin, the cornerstone of therapy, or a TZD.\textsuperscript{7} Despite their attractive efficacy, as demonstrated by A1c reductions of approximately 0.8 and 1.5\% for exenatide twice daily and liraglutide once daily respectively, their associated weight loss, and unique multifactorial mechanism of action, the safety profile of GLP-1R agonists emerges
as a concern. Efficacy, tolerability, and their adverse effect profiles, are some of the key parameters considered when initiating and titrating medication therapy. Clinical trials and post-marketing surveillance for both exenatide and liraglutide have demonstrated concerns with patient tolerability and safety, specifically in regards to gastrointestinal intolerances, pancreatitis, and the possibility of thyroid malignancies. The purpose of this article is to review the safety profile of GLP-1R agonists and to educate the pharmacist regarding recommendations for their safe use in the treatment of diabetes.

GASTROINTESTINAL INTOLERANCES

Gastrointestinal (GI) disturbances, specifically nausea and vomiting, are the most common treatment emergent side effects associated with the use of GLP-1R agonists. These GI side effects are most commonly experienced upon medication initiation and dose escalations. In most cases, GLP-1R agonist induced nausea and vomiting was transient and classified as mild to moderate. The nausea associated with GLP-1R agonists is thought to be related to a multitude of effects, including peak drug concentrations at the time of medication exposure, slowed gastric emptying, and stimulation of neutral GLP-1R receptors. In several studies, GLP-1R agonist associated nausea and vomiting were reported at a higher incidence than non-GLP-1R agonist comparators, such as sulfonylureas, metformin, and TZDs. The LEAD-6 study, which compared exenatide 5 mcg twice daily titrated up to 10 mcg twice daily after 4 weeks, to liraglutide 0.6 mg titrated up to 1.8 mg after 2 weeks, demonstrated the duration of GLP-1R agonist induced nausea and vomiting was prolonged with shorter acting agents. In this study, the majority of the liraglutide-treated patients were nausea-free by week 6, compared to week 22 for the twice daily exenatide group. Similarly, in the DURATION-1 trial, which evaluated 2 mg exenatide once weekly to 10 mcg exenatide twice daily, a significantly less proportion of patients experienced treatment related nausea with the long –acting formulation when compared to twice-daily administration. Clinical trials report the incidence of nausea between 33 – 57.1% and of vomiting between 12 – 17.4% for exenatide 10 mcg twice daily. Nausea rates observed in phase 3 trials of liraglutide 1.8mg daily, were less than those reported with twice daily exenatide and ranged from 7 – 40%. For some individuals, the GI disturbances limited the use of GLP-1R agonist therapy, as witnessed by the GI-induced discontinuation rates of 3 – 9% for exenatide 10 mcg twice daily. Strategies to prevent or alleviate GI intolerances associated with GLP-1R agonists include titrating doses conservatively after initiating therapy. For exenatide, if nausea occurs upon dosage escalation, maintenance at the lower initial dose of 5 mcg twice daily is appropriate; however, for liraglutide the target dose should be at least 1.6 mg daily, as lower doses are ineffective for glycemic control. Patients should also be counseled that nausea is most often transient, to eat smaller meals to prevent gastrointestinal intolerances, and, if on exenatide twice daily, to administer the injection immediately prior to meal-time.

One of the mechanisms by which GLP-1R agonists lower post-prandial glucose concentrations is by delaying gastric emptying. As a result, GLP-1R agonists may not be appropriate for individuals with gastroparesis, an autonomic disorder often complicated by hyperglycemia. Exenatide use is not recommended in patients with gastroparesis. While the product information for liraglutide does not currently provide any recommendations for its use in patients with gastroparesis secondary to insufficient data, the medication guide for Liraglutide instructs patients to inform their healthcare provider if they have or experience symptoms of gastroparesis.

HYPOGLYCEMIA

The possibility of hypoglycemia is an ongoing concern for medications with insulin secreting properties, such as GLP-1 agonists, sulfonylureas, and meglitinides, as well as insulin. In clinical trials the incidence of hypoglycemia amongst treatment groups for both exenatide and liraglutide were generally comparable to placebo; and when mild to moderate hypoglycemia was noted, it was associated with sulfonylurea use. Furthermore, despite the improved glycemic outcomes of the long-acting agents, the risk of hypoglycemia with liraglutide daily and exenatide once weekly was less than that observed with sulfonylureas and twice daily exenatide. It is hypothesized that the lower risk of hypoglycemia with GLP-1R agonists is related two distinct characteristics. One characteristic is its’ glucose-dependent mechanism of action. The other is the fact that when an individual’s blood glucose concentration is <65mg/dl (hypoglycemia), GLP-1R agonists do not inhibit the secretion and action of glucagon, thus allowing for a rise in glucose. Although, the 2009 American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) diabetes management algorithm classifies GLP-1R agonists as less validated tier 2 therapies, it recommends these medications, particularly exenatide (the only FDA-approved GLP-1R agonist at the time of algorithm publication) as a preferred adjunctive therapy for those individuals with hazardous employment, such as vehicle or machinery operators (i.e. truck, bus, or forklift drivers and airline pilots, etc.) or construction workers in whom hypoglycemia is less desired. In clinical trials, patients treated with exenatide monotherapy experienced mild to moderate hypoglycemia at a rate of 4-9%, while 0-12% of patients on liraglutide experienced mild to moderate hypoglycemia, which was lower than the incidence observed with glimepiride monotherapy, where hypoglycemia occurred in 24% of patients. However, due to the hypoglycemic risk with concomitant therapy, the prescribing information for GLP-1R agonists includes a recommendation to reduce the dose of secretagogues when used in combination. Presently, only exenatide is FDA-approved for combination therapy with insulin glargine. Its prescribing information, likewise recommends considering a dosage reduction for the insulin dose, which should be considered upon GLP-1R agonist initiation and dose escalation to lower the risk of hypoglycemia.
PANCREATITIS AND PANCREATIC CANCER

Post-marketing surveillance reports of acute pancreatitis in patients treated with exenatide prompted the FDA to investigate the causality, and subsequently include pancreatitis as a precaution to the product information for GLP-1R agonists (both exenatide and liraglutide). Thirty cases of exenatide-induced acute pancreatitis and six cases of hemorrhagic or necrotizing pancreatitis were cited in the FDA Adverse Reporting System (AERS) in 2008.5 A retrospective chart review utilizing the AERS database was conducted between 2004 and the third quarter of 2009 to determine if there is sufficient data correlating pancreatitis to exenatide use.17,18 Although there were several limitations to the methodology used, the study found a >6-fold increase in the risk of pancreatitis with the exenatide group when compared to the control group (which consisted of patients treated with TZD’s, rosiglitazone and two meglitinides: nateglinide and repaglinide).7,18 These findings however, were inconsistent with other data analyses and retrospective reviews, which reported similar incidences of proposed exenatide-induced pancreatitis to the comparators used17,18 One of these studies, a retrospective review of pharmacy claims data, evaluated the incidence of pancreatitis over a one-year period of 28,000 prescriptions. In this study, 0.13% of the patients treated with exenatide experienced acute pancreatitis, which was comparable to rates observed with other diabetes treatments, such as metformin or sulfonylureas.19 An additional concern is the risk association between pancreatitis and pancreatic cancer. Regarding pancreatic cancer event rates, the FDA AERS study found a 2.9-fold increase when compared to control agents.18

Regarding possible liraglutide-induced pancreatitis, in clinical trials a total of 7 cases were reported, including acute pancreatitis, chronic pancreatitis, and necrotizing pancreatitis with deaths occurring in five, two, and one case(s), respectively.5 The overall occurrence of pancreatitis was higher in the liraglutide-treated group than that observed with the comparator agents (2.2 vs. 0.6 cases per 1000-patient-years).6 Despite these reports, an absolute causation of GLP-1R agonists and pancreatitis has been difficult to establish, as both diabetes and obesity are associated with their own risks of pancreatitis. The risk of developing pancreatitis in an individual with T2DM confers a 2.8-fold increase when compared to individuals without T2DM.15 Obese individuals with T2DM are likely to be prescribed a GLP-1R agonist due to a positive impact on weight reduction and glycemic control; however, these patients are also at a high risk of developing pancreatitis secondary to their concomitant medical conditions. Other risk factors for pancreatitis are hypertriglyceridemia, excessive alcohol intake, gallstones, and history of pancreatitis.20 Specific to exenatide therapy, the incidence of pancreatitis was observed upon dose escalation to 10 mcg twice a day.20 Recommendations are to observe patients for pancreatitis after a dose escalation for both products.20

Both exenatide and liraglutide have boxed warnings in their label information regarding pancreatitis.5,6 As a mandate from the FDA, Amylin Pharmaceuticals Inc. must conduct six post-marketing studies on exenatide to further explore the mechanism, incidence, and risk factors for the development of acute pancreatitis with and without hemorrhagic and necrotizing complications.20

Practitioners should exercise caution when prescribing GLP-1R agonists for patients at risk of developing pancreatitis and should educate patients of warning signs of pancreatitis and inform them to immediately discontinue therapy and seek medical attention if pancreatitis is suspected.22 If pancreatitis is confirmed, GLP-1 therapy should not be re-initiated.3,5 This is a key educational parameter that should be reinforced by the pharmacist upon medication dispensing.

THYROID

The development of malignant thyroid tumors was found in pre-clinical animal studies amongst rodents who received liraglutide doses that were 8 times higher than the recommended human doses.6,23 In clinical trials, 5 cases of papillary thyroid carcinoma occurred in liraglutide-treated patients, compared to 1 case reported in the non-liraglutide group.5 These findings raised concerns about the development of C-cell hyperplasia and medullary thyroid cancer in humans, prompting the prescribing information for liraglutide to carry a boxed warning for thyroid C-cell hyperplasia.23 Although this specific type of cancer is rare in humans, and the FDA warning states that the human relevance of these findings is unclear, liraglutide therapy is contraindicated in patients with a family history of medullary thyroid cancer or in patients with a history of multiple endocrine neoplasia syndrome 2.6 The proposed mechanism by which liraglutide causes C-cell hyperplasia, and possibly cancer, is through increased stimulation of calcitonin release, which is a biomarker for medullary cancer. A 2-year study evaluating calcitonin concentrations in liraglutide-treated patients did not show a difference when compared to other anti-diabetes medications; however, when compared to placebo, concentrations were elevated.21,22 In an effort to attain definitive information regarding the association of liraglutide and thyroid cancer in humans, the FDA has mandated that the manufacturer, Novo Nordisk, institute two surveillance systems. One is to establish a cancer registry to monitor the incidence of medullary thyroid cancer over the next 15 years and the other is to conduct a 5-year epidemiological study, using a large healthcare claims database, to compare the development of thyroid cancer among liraglutide-treated patients to those who are liraglutide naïve.21,23

The FDA AERS database study also evaluated the present data correlating thyroid cancer to exenatide use.18 It found a statistically significant increase of thyroid cancer in the exenatide-treated group.18 Therefore,
Amylin Pharmaceuticals Inc. acknowledges the presence of benign C-cell tumors in rats treated with the exenatide, and has included this information in the package insert.5

ALTERED KIDNEY FUNCTION

Post-marketing reports of both altered and worsening kidney function exist for both exenatide and liraglutide. In November 2009, the FDA released information for healthcare professionals regarding 78 cases of altered kidney function associated with exenatide therapy.24 Between April 2005 and October 2008, 62 cases of acute renal failure and 16 cases of renal insufficiency were noted. Although some cases were reported in individuals with pre-existing renal disease or with at least one risk factor for kidney disease, revisions were made to the product labeling regarding the evaluation for and dosing in kidney dysfunction.24 The product information for liraglutide acknowledges post-marketing reports of increased serum creatinine, acute renal failure, and the development or worsening of chronic renal failure, which in some cases, required hemodialysis.6 Unlike exenatide however, liraglutide is not renally excreted and does not require renal dosage adjustments.5 Common GLP-1R associated side effects, including nausea, vomiting, diarrhea, and subsequent dehydration, may increase the risk of kidney abnormalities.5,6 Exenatide and liraglutide manufacturers recommend caution when initiating or increasing the dose in patients with renal impairment.5,6

REMS

The Risk Evaluation and Mitigation Strategy (REMS), was developed by the FDA in an effort to be proactive on patient safety measures once a medication concern is identified. The REMS program is designed to provide both practitioners and patients with information regarding medication safety concerns. In most cases, the REMS will include a communication plan for practitioners and a medication guide for patients. Practitioner information highlights safety considerations, current findings, and makes recommendations regarding appropriate pharmacotherapy for specific patient populations. The patient medication guide informs the individual about possible risk(s), warning signs, and appropriate action to take in the event of a concern. Both exenatide and liraglutide have a REMS. Table 2 outlines the REMS with these agents.

Table 2: Overview of REMS with Exenatide & Liraglutide20,24

<table>
<thead>
<tr>
<th>Safety Concerns</th>
<th>REMS Requirements</th>
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<tbody>
<tr>
<td>Pancreatitis / Pancreatic Cancer</td>
<td>Exenatide</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>n/a</td>
</tr>
<tr>
<td>Kidney Impairment</td>
<td>✓</td>
</tr>
</tbody>
</table>

Recent advances in the understanding of the pathogenesis of diabetes have focused on the multiple hormonal deficiencies that result in clinical hyperglycemia. The GLP-1R agonists represent a novel class of treatment agents that add promise to the diabetes treatment armamentarium, as they target these underlying hormonal defects, and may even have the potential to delay disease progression by preserving beta-cell functioning.2,4 Despite their overall benefit on glycemic control, widespread use may be limited by their toxicity profiles. Health care practitioners, including pharmacists, should be aware of treatment-related toxicities, and assess the risk vs. benefit when initiating or escalating therapy with these agents. A clear understanding of patient risk factors for the development of adverse effects, as well as familiarity with the signs and symptoms of potential treatment-related toxicities can aid in disease management. In summary, the GLP-1R agonists can provide an effective means for glycemic control, when used in the proper clinical situation.
REFERENCES


2. Drucker DJ. The biology of incretin hormones Cell Metabolism 2006;3; 153-165


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CE Test Questions

1. Glucagon like peptide-1 (GLP-1) are peptide hormones secreted from the: (Objective 1)
   a. Gastrointestinal tract
   b. Kidney
   c. Liver
   d. Muscle
   e. Pancreas

2. Which of the following mechanisms play a role in the development of type 2 diabetes? (Objective 1)
   a. Abnormal glucagon production
   b. Altered hepatic gluconeogenesis
   c. Decreased insulin secretion
   d. Increased insulin resistance
   e. All of the above

3. Which of the following statements are TRUE regarding GLP-1 agonists and the side effect of nausea? (Objective 3)
   a. Commonly experienced upon medication initiation
   b. Commonly experienced upon dose escalation
   c. Often transient and classified as mild to moderate
   d. Occurs at a higher rate with GLP-1 agonist compared to other cornerstone therapies
   e. All of the above

4. According to the manufacturer recommendations, which of the following medications should be adjusted by a dosage reduction upon initiation of GLP-1 agonist in an effort to decrease the incidence of hypoglycemia? (Objective 3,5)
   a. Glipizide
   b. Insulin
   c. Nateglinide
   d. a and b
   e. all of the above

5. HB, 55-year old female with type 2 diabetes and mild renal impairment, recently completed 2 weeks of liraglutide therapy. Her practitioner is interested in increase her dose from 1.2 mg daily to 1.6 mg daily. Which of the following GLP-1 agonist associated side effects should be evaluated upon the dosage increase? (Objective 3)
   a. Thyroid Cancer
   b. Pancreatitis
   c. Kidney Dysfunction
   d. b and c
   e. All of the above

6. The proposed mechanism for C-cell hyperplasia and papillary thyroid carcinoma is: (Objective 5)
   a. Currently unknown
   b. Induction dehydration secondary to nausea, vomiting, and diarrhea
   c. Inhibition of glucagon release
   d. Stimulation of calcitonin release
   e. Stimulation of β-cells on the thyroid gland

7. Both exenatide and liraglutide require a REMS for which of the following safety concerns? (Objective 4)
   a. Hypoglycemia
   b. Nausea and vomiting
   c. Pancreatitis
   d. Thyroid Cancer
c. Kidney Impairment

8. Patients with which of the following medical conditions and/or factors should not be a candidate for GLP-1 agonist therapy? (Objective 3,5)
   a. Gastroparesis
   b. Moderate creatinine clearance (30 – 50 ml/min)
   c. Machinery operator (i.e. airline pilot)
   d. Family history of hypertriglyceridemia
   e. Metformin use

9. In the glycemic control algorithm developed by the American Association of Clinical Endocrinologist and the American College of Endocrinology (AACE/ACE), GLP-1 agonists are recommended as 1st line therapy particularly for individuals with which of the following conditions/factors? (Objective 1)
   a. Elevated fasting blood glucose concentrations
   b. Elevated post-prandial blood glucose concentrations
   c. BMI > 40 kg/m²
   d. b and c
   e. all of the above