Lixisenatide: A New Option for Managing Type 2 Diabetes

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Abstract

Objective: To evaluate the clinical role of Adlyxin (lixisenatide) in the treatment of type 2 diabetes mellitus. **Data Sources:** A MEDLINE search of the English language indexed from January 2013 to April 2017 was conducted using the search terms lixisenatide, safety, and efficacy. **Study Selection and Data Extraction:** Studies including human subjects were utilized to assess the efficacy and safety of lixisenatide. **Data Synthesis:** Lixisenatide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying. Clinical trials demonstrate that lixisenatide is an effective add-on pharmacotherapy option to achieve goal HbA1c levels. For example, in the Get Goal-Duo 1 study, HbA1c decreased to 7.0% in the lixisenatide group versus 7.3% in the placebo group (least square mean difference of -0.3% , $P < .0001$). Furthermore, lixisenatide was shown to be superior to liraglutide in reducing postbreakfast glucose levels. **Conclusions:** Clinical studies have demonstrated that lixisenatide is a safe and effective treatment option for type 2 diabetes mellitus. In addition, it may be a safer and equally effective option to rapid-acting insulin.

Keywords

diabetes, GLP-1 RA, lixisenatide, safety, efficacy

Introduction

According to the World Health Organization, the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014.¹ In the United States, approximately 29.1 million Americans have diabetes with an estimated 1.4 million new cases per year.² Globally in 2012, approximately 1.5 million deaths were attributed to diabetes and another 2.2 million deaths were attributable to hyperglycemia.¹ Furthermore, diabetes is the seventh leading cause of death in the United States.³ If untreated, diabetes can result in numerous complications such as chronic kidney disease, retinopathy, amputations, as well as cardiovascular disease. It is a complex disease state that is multifactorial. There are several risk factors associated with type 2 diabetes including family history, age, hypertension, dyslipidemia, and overweight and obesity.⁴ Due to the various risk factors associated with diabetes, new and comprehensive therapies are constantly being studied. An effective pharmacologic treatment option is the glucagon-like peptide-1 (GLP-1) receptor agonists (RAs).

Since 2005, there have been 5 GLP-1 RAs approved to treat type 2 diabetes in the United States.⁵ Lixisenatide (Adlyxin), the most recently approved GLP-1 RA, has proven to be a promising agent for patients with postprandial

blood glucose excursions. Manufactured by Sanofi Aventis, lixisenatide was approved by the Food and Drug Administration in July 2016 for the treatment of type 2 diabetes. A MEDLINE search of the English language indexed from January 2013 to April 2017 was conducted using the search terms lixisenatide, safety, and efficacy. This article will provide a comprehensive review of lixisenatide and its role in pharmacy practice.

Data Sources

A MEDLINE literature search was performed in order to identify articles addressing the safety and efficacy of using lixisenatide in patients with type 2 diabetes. The search was conducted using the search terms lixisenatide, safety, and efficacy. Search limits included human studies published in English. The literature search extended from January 2013 to April 2017. Additional references were identified from a review of literature citations.

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Pharmacology and Pharmacokinetics/ Pharmacodynamics

Lixisenatide is a GLP-1 RA that increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.⁶ Lixisenatide is a synthetic analog of exendin-4, an endogenous glucagon-like protein-1. Unlike exendin-4, lixisenatide contains a C-terminal modification of the addition of 6 lysine residues and deletion of a proline.⁶ It has a 4-fold higher binding affinity for the GLP-1 receptor compared to native GLP-1.⁶ Lixisenatide is considered a short-acting GLP-1 RA compared to other long-acting GLP-1 RAs such as liraglutide and once-weekly exenatide due to its short half-life. Although its half-life is only 3 hours, its increased binding affinity in conjunction with its ability to delay gastric emptying allows it to be dosed once daily.⁶ Furthermore, the ability of the drug to significantly delay gastric emptying results in satiety, which contributes to weight loss. Following subcutaneous administration, the median T_{max} , which is the time needed to reach maximum concentration, is 1 to 3.5 hours independent of injection site (abdomen, thigh, or arm).⁷ Age, body weight, gender, and race appears to have no effect on the pharmacokinetics of lixisenatide.⁷ The plasma C_{max} , which is the maximum plasma concentration after oral dosing, is significantly increased in patients with renal impairment. In a small study of patients, the plasma C_{max} increased by approximately 60%, 42%, and 83% in participants with mild (creatinine clearance [CrCl] 60–89 mL/min), moderate (CrCl 30–59 mL/min), and severe (CrCl 15–29 mL/min) renal impairment, respectively. However, in patients with mild to severe chronic kidney disease, the manufacturer does not recommend dosage adjustments.⁷ Due to the lack of therapeutic evidence in patients with end-stage renal disease, the manufacturer recommends against using lixisenatide in patients with a CrCl < 15 mL/min. The pharmacokinetics of lixisenatide is not expected to be affected by hepatic impairment.

The pharmacodynamics of lixisenatide have been established via studies including patients with uncontrolled type 2 diabetes taking metformin, sulfonylureas, or both.^{8,9} Seino et al⁸ evaluated the efficacy, safety, and pharmacodynamics of lixisenatide in Japanese and Caucasian patients with type 2 diabetes insufficiently controlled with sulfonylureas with or without metformin. Patients were randomized to receive lixisenatide twice daily, lixisenatide once daily, or matching placebo within each ethnicity for 5 to 6 weeks. The primary end point was to assess the change in postprandial glucose (PPG) area under the curve (AUC) after a standardized breakfast from baseline to the last day of the study at the highest well-tolerated dose. The standardized breakfast was a 500 kcal meal including orange juice, toasted bread, jam or preserves, butter or margarine, whole milk, and coffee or tea with nonnutritive sweetener if desired. One of the

secondary end points included evaluating the influence of ethnicity on increasing once-daily or twice-daily doses of lixisenatide on PPG AUC after a standardized breakfast in Japanese and Caucasian patients. Another essential secondary end point consisted of examining the change from baseline in PPG AUC and 2-hour PPG after a standardized breakfast on the last day of lixisenatide at 10, 20, and 30 µg doses or on the last day at the highest tolerated dose. Additional secondary end points included change from baseline in fasting plasma glucose (FPG), HbA1c, and body weight. For the primary end point, the least square (LS) mean differences in PPG AUC were –333.4 and –288.8 h mg/dL for lixisenatide once daily and twice daily compared to placebo, respectively. Based on the secondary data end points, Japanese patients experienced a significantly greater reduction in PPG AUC after a standardized breakfast when treated with lixisenatide compared to Caucasian patients. Reductions in FPG and HbA1c were statistically significant in patients receiving lixisenatide; however, changes in body weight did not reach statistical significance.

Kapitza et al⁹ assessed the pharmacodynamics characteristics of lixisenatide once daily versus liraglutide once daily in patients with type 2 diabetes insufficiently controlled on metformin (≥ 1.5 g/day). Subjects were randomized to receive either once-daily lixisenatide treatment or once-daily liraglutide treatment. The primary efficacy end point was to evaluate the change in the area under the plasma glucose concentration-time curve in the 4-hour period after the start of the standardized breakfast test meal from baseline to day 28 of the study. Secondary efficacy measures included changes in the maximum PPG excursion after the standardized breakfast test meal, premeal-corrected AUC for serum insulin, serum C-peptide and plasma glucagon levels, 24-hour plasma glucose, and mean HbA1c. Based on the results, lixisenatide was superior to liraglutide in controlling postprandial glucose. Lixisenatide provided a significantly greater reduction in PPG, maximum PPG excursion, postprandial glucagon levels, as well as plasma glucose levels during the postbreakfast period (~45 minutes to ~4 hours after drug administration). However, plasma glucose levels were lower for liraglutide than for lixisenatide when considering all time points (eg, 4.5 hours after drug administration, before breakfast, etc). Furthermore, lixisenatide resulted in significantly reduced levels of postprandial insulin and C-peptide versus liraglutide.

Dosing and Administration

Lixisenatide is dosed at either 10 µg (starter dose) or 20 µg (maintenance dose). It is administered subcutaneously as a clear solution packaged in 3-mL prefilled pens. The 10 µg/dose pen contains 50 µg/mL in a green single-patient use pen, and the 20 µg/dose pen contains 100 µg/mL in a

burgundy single-patient use pen. Each pen delivers 14 doses and should be discarded 14 days after first use. Prior to first use, lixisenatide should be refrigerated but not frozen. The patient should be counseled to replace the pen cap after each use to protect from light.

Clinical Efficacy

Versus Placebo

Clinically lixisenatide has proven to be an effective add-on agent for patients uncontrolled on basal insulin, metformin, sulfonylureas, or pioglitazone as well as a viable alternative to rapid-acting insulin (refer to Table 1). The GetGoal-Duo 1 study¹⁰ analyzed adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine. In this phase III, randomized, double-blind, placebo-controlled study, patients were assigned to add either lixisenatide or injectable placebo to their current regimens. The primary efficacy measure was the absolute change of HbA1c from baseline to week 24. Secondary efficacy variables included the change from baseline to week 24 in 2-hour PPG and blood glucose excursions, 7-point plasma-calibrated self-measurement of plasma-referenced glucose (SMPG), FPG, body weight, and average daily insulin glargine dosage. After 24 weeks, HbA1c decreased to 7.0% in the lixisenatide group versus 7.3% in the placebo group (LS mean difference of -0.3% , $P < .0001$). In addition to a statistically significant decrease in absolute change of HbA1c, more patients achieved an HbA1c of less than 7% or 6.5% in the lixisenatide group versus the placebo group ($P = .0001$ and $P < .0001$, respectively). With regard to the secondary efficacy measures, SMPG values were reduced significantly ($P = .0071$) with lixisenatide specifically after the morning meal and a significant reduction in body weight was demonstrated in the lixisenatide group ($P = .0012$). There was an increase in insulin dose seen in both groups and there was no significant change in FPG from baseline.

GetGoal-L¹¹ examined adding once-daily lixisenatide for type 2 diabetes in patients inadequately controlled by established basal insulin. Similar to GetGoal-Duo 1, this study focused on the change in HbA1c from baseline to week 24 as well as the percentage of patients attaining the goal HbA1c, change in FPG, body weight, SMPG, 2-hour PPG after a standardized meal and glucose excursion, daily basal insulin dosage, and percentage of participants requiring rescue therapy. At the conclusion of week 24, mean HbA1c declined significantly from $8.4 \pm 0.9\%$ at randomization to $7.8 \pm 1.2\%$ in the lixisenatide group compared to $8.4 \pm 0.8\%$ to $8.1 \pm 1.2\%$ in the placebo group ($P = .0002$). A higher percentage of patients in the lixisenatide achieved the goal HbA1c. Comparable to GetGoal-Duo 1, the main reduction in SMPG was seen 2 hours postbreakfast with the

smallest reduction before breakfast. Participants had a significant reduction in body weight ($P < .0001$) with lixisenatide compared to placebo; however, change in mean FPG was insignificant.

GetGoal-M¹² studied the efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin. Participants were placed into 1 of 4 treatment arms: lixisenatide or placebo injection in the morning or lixisenatide or placebo injection in the evening. The 2 most important end points were the absolute change in HbA1c from baseline to week 24 in the morning and evening injection treatment arms. Other measures included the percentage of patients achieving HbA1c $< 7.0\%$ or $\leq 6.5\%$, change in body weight, change in 2-hour PPG and glucose excursion after a standardized breakfast meal, β -cell function, and the percentage of patients who required rescue medication. The mean HbA1c was significantly reduced by both the lixisenatide morning and evening injections compared to placebo ($P < .0001$ for morning and evening injections). In addition, more participants achieved an HbA1c of $< 7.0\%$ or $\leq 6.5\%$ in the lixisenatide group compared to placebo. There was a significant reduction observed in FPG, 2-hour PPG, as well as in glucose excursion in the lixisenatide group (refer to Table 1). Furthermore, there was an improvement in β -cell function and positive decreases in body weight.

GetGoal-M-Asia¹³ studied similar outcomes as GetGoal-M but with a focus on the Asian population. In addition, GetGoal-M-Asia compared once-daily lixisenatide and placebo in patients inadequately controlled on metformin with or without a sulfonylurea. At the conclusion of the study, lixisenatide treated patients had a lower HbA1c and a higher percentage of patients reach the goal HbA1c versus placebo treated patients. There was improvement in postprandial glucose after a standardized breakfast and in FPG, however no statistical difference in body weight following the 24 weeks.

GetGoal-P¹⁴ examined the efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone with or without metformin. The primary efficacy end point was the absolute change in HbA1c after 24 weeks. Additional measures studied in the trial were percentage of patients to reach a goal HbA1c, change in FPG, body weight, β -cell function, fasting plasma insulin, and percentage of patients needing rescue therapy. Similar to other studies, significant improvement was observed in absolute change in HbA1c and percentage of patients achieving a goal HbA1c. Change in β -cell function was similar between the 2 groups, and although statistically insignificant, lixisenatide had a small decrease in body weight versus a small increase with placebo. The decrease in body weight associated with lixisenatide may be useful in counteracting the weight gain associated with thiazolidinediones.

Table 1. Clinical efficacy trials for lixisenatide versus placebo.

	Patient Population	Study Design	Efficacy Outcomes	LS Mean Difference Versus Placebo (P vs Placebo)
GetGoal-Duo 1 (<i>Insulin glargine + metformin</i> [$\pm$ TZDs] + placebo vs <i>insulin glargine + metformin</i> [$\pm$ TZDs] + lixisenatide)	Adults with type 2 diabetes	Phase III, randomized, double-blind, placebo-controlled, parallel-group protocol	Primary:	Primary:
	Inclusion: use of metformin for at least months alone or in combination with a sulfonylurea or glinide, or thiazolidinedione; HbA1c $\geq 7.0\%$ and $\leq 10\%$; BMI $> 20 \text{ kg/m}^2$		<ul style="list-style-type: none"> Absolute change of HbA1c (%) from baseline to week 24 	<ul style="list-style-type: none"> -0.3 ($P < .0001$)
GetGoal-L (<i>Basal insulin</i> [$\pm$ metformin] + placebo vs <i>basal insulin</i> [$\pm$ metformin] + lixisenatide)	Adults with type 2 diabetes (≥ 1 year)	Phase III, randomized, placebo-controlled, 2-arm, parallel-group, double-blind	Secondary: <ul style="list-style-type: none"> Change from baseline to week 24 in 2-hour PPG (mmol/L) and blood glucose excursions (mmol/L) Change in 7-point plasma-calibrated SMPG (mmol/L) Change in FPG (mmol/L) Change in body weight (kg) Average daily insulin glargine dosage (units/day) Additional secondary: <ul style="list-style-type: none"> Percentage to achieve HbA1c <ul style="list-style-type: none"> $< 7\%$ $\leq 6.5\%$ 	Secondary: <ul style="list-style-type: none"> -3.2 ($P < .0001$) -3.1 ($P < .0001$) -0.4 ($P = .0071$) -0.1 ($P = .5142$) -0.9 ($P = .0012$) -2.2 ($P = .03$) $P = .0001$ $P < .0001$
	Inclusion: use of a basal insulin regimen for at least 3 months; HbA1c equal 7% to 10%		Primary: <ul style="list-style-type: none"> Change in HbA1c from baseline to week 24 (%) 	<ul style="list-style-type: none"> -0.4 ($P = .0002$)
			Secondary: <ul style="list-style-type: none"> Percentage to achieve HbA1c <ul style="list-style-type: none"> $< 7\%$ $\leq 6.5\%$ Change from baseline in <ul style="list-style-type: none"> FPG (mmol/L) Body weight (kg) 	<ul style="list-style-type: none"> $P < .0001$ $P = .0003$ -0.1 ($P = .7579$) -1.3 ($P < .0001$)

(continued)

Table 1. (continued)

Patient Population	Study Design	Efficacy Outcomes	LS Mean Difference Versus Placebo (P vs Placebo)
GetGoal-M (Lixisenatide morning injection vs lixisenatide evening injection vs placebo)	Patients with type 2 diabetes inadequately controlled on metformin (1.5 g/day) for at least 3 months; HbA1c 7% to 10% group	<ul style="list-style-type: none"> Seven-point plasma calibrated SMPG (mmol/L) 2-hour PPG (mmol/L) Glucose excursion (mmol/L) Change in daily basal insulin dosage (units/day) Primary: <ul style="list-style-type: none"> Absolute change in HbA1c from baseline to week 24 (morning lixisenatide dose, %) Secondary: <ul style="list-style-type: none"> Absolute change in HbA1c from baseline to week 24 (evening lixisenatide dose, %) Change from baseline to week 24 in percentage to achieve HbA1c <7% 	<ul style="list-style-type: none"> -0.9 ($P < .0001$) -3.8 ($P < .0001$) -3.8 ($P < .0001$) -3.7 ($P = .0120$)
GetGoal-M-Asia (Lixisenatide + metformin [$\pm$ sulfonylurea] vs placebo + metformin [$\pm$ sulfonylurea])	Asian participants with type 2 diabetes; inadequately controlled on metformin with or without sulfonylurea; HbA1c $\geq 7.0\%$ and $< 10.0\%$ group, multinational	<ul style="list-style-type: none"> Morning Evening $\leq 6.5\%$ <ul style="list-style-type: none"> Morning Evening FPG (mmol/L) <ul style="list-style-type: none"> Morning Evening Body weight (kg) <ul style="list-style-type: none"> Morning Evening 2-hour PPG (mmol/L) Primary: <ul style="list-style-type: none"> Absolute change in HbA1c from baseline to week 24 (%) 	<ul style="list-style-type: none"> $P < .0001$ $P < .0001$ $P = .0003$ $P = .012$ -0.9 ($P < .0001$) -0.6 ($P = .0046$) Not statistically significant -4.5 ($P < .0001$) -0.36 ($P = .0004$)

(continued)

Table 1. (continued)

	Patient Population	Study Design	Efficacy Outcomes	LS Mean Difference Versus Placebo (P vs Placebo)
GetGoal-P	Adults with type 2 diabetes; treated with pioglitazone (≥ 30 mg/day) with or without metformin for at least 3 months; HbA1c $\geq 7.0\%$ and $\leq 10.0\%$	Phase III, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter, multinational study	<p>Secondary:</p> <ul style="list-style-type: none"> Percentage to achieve HbA1c <ul style="list-style-type: none"> $< 7\%$ $\leq 6.5\%$ Change from baseline in <ul style="list-style-type: none"> FPG (mmol/L) Body weight (kg) 2-hour PPG (mmol/L) Glucose excursion (mmol/L) <p>Primary:</p> <ul style="list-style-type: none"> Absolute change in HbA1c from baseline to week 24 (%) Percentage to achieve HbA1c <ul style="list-style-type: none"> $< 7\%$ $\leq 6.5\%$ <p>Secondary:</p> <ul style="list-style-type: none"> Change from baseline in <ul style="list-style-type: none"> FPG (mmol/L) Body weight (kg) 	<ul style="list-style-type: none"> $P = .003$ $P = .001$ -4.8 ($P = .0109$) $P = .296$ -4.28 ($P < .0001$) -3.99 -0.56 ($P < .0001$) $P < .0001$ $P < .0001$ -0.84 ($P < .0001$) -0.41 ($P = .1864$)

Abbreviations: LS, least squared; BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial glucose; SMPG, self-measurement of plasma-referenced glucose.

Head to Head

Meier et al¹⁵ contrasted the effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin. Study participants were assigned to receive lixisenatide 20 µg once daily, liraglutide 1.2 mg once daily, or liraglutide 1.8 mg once daily as add-on therapy to insulin glargine for 8 weeks. Patients taking metformin were continued on the same dose throughout the trial. The primary end point was the change in premeal adjusted AUC PPG from the start of a standardized breakfast until 4 hours later. Secondary end points included change in premeal adjusted glucagon and premeal adjusted C-peptide AUC, HbA1c, FPG, body weight, and 24-hour plasma glucose profiles. At the conclusion of 8 weeks, lixisenatide significantly reduced the AUC PPG more than both liraglutide doses ($P < .001$). The 24-hour plasma glucose profiles were comparable across the 3 treatment arms; however, the greatest reduction with lixisenatide was seen postbreakfast. Liraglutide controlled glucose throughout the day more effectively than lixisenatide. Gastric emptying was significantly longer with lixisenatide compared to the liraglutide arms ($P < .001$).

The GetGoal-X trial¹⁶ examined the efficacy and safety of lixisenatide once daily versus exenatide twice daily in patients with type 2 diabetes uncontrolled on metformin. Participants were either randomized to lixisenatide or exenatide. The primary outcome was the absolute change in HbA1c from baseline to week 24. The secondary outcome assessed the percentage of patients to achieve a goal HbA1c of $<7.0\%$ or $\leq 6.5\%$ at week 24 as well as changes in FPG and body weight. Based on the data, the authors concluded that lixisenatide was noninferior to exenatide. Lixisenatide and exenatide had similar reductions in A1c, FPG, as well as body weight.

Nauck et al¹⁷ compared once-daily liraglutide to lixisenatide as add-on to metformin in type 2 diabetes patients. The study was a 26-week randomized controlled trial that assigned participants to take liraglutide 1.8 mg or lixisenatide 20 µg. At the conclusion of the study, liraglutide was deemed to be superior based on a greater reduction in HbA1c ($P < .0001$). Liraglutide was more effective in lowering FPG ($P < .0001$); however, morning injection lixisenatide resulted in a lower after-breakfast postprandial increment ($P < .0001$).

Rosenstock et al¹⁸ tested lixisenatide plus basal insulin versus insulin glulisine either as a basal-plus or basal-bolus in patients with type 2 diabetes. Patients were randomized to receive lixisenatide once daily in addition to insulin glargine or insulin glulisine once or thrice daily added to insulin glargine. The authors concluded that lixisenatide was noninferior to glulisine with regard to glucose control but superior in body weight reduction. Furthermore, the

lixisenatide group experienced less symptomatic hypoglycemia episodes.

Clinical trials demonstrate that lixisenatide is more effective in controlling postprandial glucose excursions (specifically after breakfast) compared to longer acting GLP-1 RAs such as liraglutide. In addition, lixisenatide may be an effective, alternative adjunct therapy with basal insulin as opposed to initiating rapid acting insulin. In November 2016, the Food and Drug Administration approved Soliqua 100/33 (insulin glargine and lixisenatide) injection for the treatment of inadequately controlled type 2 diabetes. However, lixisenatide is not as effective in controlling FPG compared to longer acting GLP-1 RAs.

Cardiovascular Disease

Nauck et al¹⁷ demonstrated that GLP-1 RAs may improve lipid levels in addition to blood glucose levels. The investigators examined the effect of liraglutide and lixisenatide by tracking changes in the patients' lipid profile. After 26 weeks, participants HDL levels were slightly increased with decreases for the rest of the lipid parameters. Although the improvements were not statistically significant, the results revealed a potential additional benefit of GLP-1 RAs. Additional studies have been conducted to assess the value of using GLP-1 RAs in patients with coronary artery disease.

The ELIXA study¹⁹ investigated the use of lixisenatide in patients with type 2 diabetes and acute coronary syndrome. The primary end point in the time-to-event analysis was a composite of any of the following: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Based on the hazard ratio for the primary end point, lixisenatide was noninferior to placebo but not superior to placebo. In comparison, in the LEADER study²⁰ liraglutide significantly lowered the rate of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus compared to placebo.

Adverse Effects, Precautions/Contraindications, and Interactions

The most common adverse reactions associated with lixisenatide include nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia.⁷ According to clinical trials, gastrointestinal adverse effects are the most prevalent specifically nausea. The gastrointestinal adverse effects present within the first 2 months of therapy but appear to be transient.¹⁰ Hypoglycemia is not common unless administered with other antidiabetic agents that cause hypoglycemia (ie, basal insulin, sulfonylureas). Lixisenatide is contraindicated in patients with known hypersensitivity to lixisenatide

or to any component it contains.⁷ Due to cases of pancreatitis being associated with lixisenatide, alternative antidiabetic therapies should be considered for patients with a history of pancreatitis. Lixisenatide should not be used in patients with diabetic ketoacidosis. Patients may develop antibodies to lixisenatide which is associated with a higher incidence of allergic reactions and injection site reactions. However, based on the GetGoal-L trial efficacy does not appear to be significantly impaired by the presence of antibodies. Lixisenatide may reduce the rate of absorption of orally administered medications due to its ability to slow gastric emptying. Individuals using oral contraceptives (OC) should take the OC 1 hour prior to lixisenatide dose or 11 hours after the lixisenatide dose. Caution should be used with coadministering lixisenatide with oral medications that have narrow therapeutic indexes. The levels of these medications should be monitored closely while administered with lixisenatide.

Conclusion and Discussion

According to the 2017 American Diabetes Association Standards of Care Guidelines,²¹ if noninsulin monotherapy at a maximum tolerated dose does not achieve or maintain the A1c target after 3 months, a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin should be added. The drug of choice should be determined by patient preferences in addition to comorbid conditions and drug characteristics. Lixisenatide would be an appropriate option for patients who are obese, have hypoglycemia unawareness, or as an alternative to prandial insulin.

Similar to other GLP-1 RAs, lixisenatide has demonstrated an ability to reduce body weight. As a short-acting GLP-1 RAs, lixisenatide can reduce body weight by 1 to 5 kg.²² This can be due to its ability to substantially decelerate gastric emptying significantly more than the long-acting (exenatide weekly or liraglutide) GLP-1 RAs. Since GLP-1 RAs glucose lowering ability are glucose dependent, they do not typically cause hypoglycemia. This mechanism makes lixisenatide and other GLP-1 RAs an appropriate option for patients with hypoglycemia unawareness. Furthermore, due to its significant reduction in gastric emptying, which results in a delayed entry of glucose into the circulation, lixisenatide is a suitable alternative to prandial insulin. Current guidelines recommend that if HbA1c remains elevated with basal insulin, consider combination injectable therapy. This includes adding one rapid-acting insulin injection before the largest meal, adding a GLP-1 RA, or changing to premixed insulin twice daily. Due to lixisenatide exceptional ability to reduce postprandial excursions (specifically after breakfast) and its weight loss advantages, it may be preferable to adding a rapid acting insulin injection.

Clinical studies have demonstrated that lixisenatide is a safe and effective treatment option for type 2 diabetes mellitus. It is noninferior to its counterparts with regard to lowering postprandial glucose excursions. In addition, it may be a safer and equally effective option to rapid-acting insulin. It has additional benefits such as body weight reduction and improving lipid levels. Although cost will be the primary issue with establishing lixisenatide as a common therapeutic option for the treatment of type 2 diabetes mellitus, it has been proven to be a valuable addition to antidiabetic pharmacotherapy.

Declaration of Conflicting Interests

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