

New Treatment Options for Type 2 Diabetes: Incretin-Based Therapy

New Treatment Options for Type 2 Diabetes: Incretin-Based Therapy is supported by an educational grant from Novo Nordisk Inc. This program has been accredited by the American Association of Diabetes Educators (AADE) for nurses, dietitians, pharmacists, and pharmacy technicians.

Susan A. Cornell, PharmD, CDE, FAPhA, FAADE



**Assistant Professor
Midwestern University
Chicago College of Pharmacy
Downers Grove, IL**

The following program is a taped presentation by Susan A. Cornell.

Susan A. Cornell is the assistant director of experiential education and an assistant professor in the department of pharmacy practice at Midwestern University Chicago College of Pharmacy in Downers Grove, Illinois. Dr. Cornell is also a clinical pharmacy consultant and certified diabetes educator, specializing in community and ambulatory care practice. She has more than 20 years of practice in community pharmacy, where she has practiced as a clinical pharmacist, diabetes educator, and preceptor, as well as the coordinator of the American Diabetes Association (ADA)-recognized Dominick's Pharmacy Diabetes Self-Management Education program.

Dr. Cornell received her bachelor of pharmacy at the University of Illinois College of Pharmacy in 1986 and her Doctor of Pharmacy at Midwestern University in May 2002.

Dr. Cornell's current clinical practice is with the Access Community Health Network, where she trains, educates, and supervises students from the colleges of medicine, pharmacy, and health sciences, as they provide diabetes education classes for patients in underserved clinics.

Dr. Cornell received the 2008 American Association of Diabetes Educators Fellow Award, 2008 American Pharmacists Association Fellow Award, 2006 Midwestern University Chicago College of Pharmacy Alumnus of the Year Award, the 2005 Midwestern University Golden Apple Teaching Award, and the 2003 Illinois Pharmacists Association Pharmacist of the Year Award.

She is an active member of the ADA and the American Association of Diabetes Educators, where she served on their board of directors from 2004 to 2007. Dr. Cornell has given numerous presentations to various health care professionals and community groups and has published and contributed to numerous professional written and online publications.

We will now join Dr. Cornell.

Program Objectives

After completing this program, participants will be able to:

- Explain major characteristics and functions of endogenous incretins
- Discuss the mechanism of action and therapeutic properties of dipeptidyl peptidase-4 (DPP-4) inhibitors
- Describe the mechanism of action and therapeutic properties of glucagon-like peptide-1 (GLP-1) agonists
- List the important patient education messages for incretin-based therapy
- Compare GLP-1 agonists and DPP-4 inhibitors with other treatment options for type 2 diabetes

After completing this program, participants will be able to:

- Explain major characteristics and functions of endogenous incretins
- Discuss the mechanism of action and therapeutic properties of dipeptidyl peptidase-4 (DPP-4) inhibitors
- Describe the mechanism of action and therapeutic properties of glucagon-like peptide-1 (GLP-1) agonists
- List the important patient education messages for incretin-based therapy
- Compare GLP-1 agonists and DPP-4 inhibitors with other treatment options for type 2 diabetes

Metabolic Defects in Type 2 Diabetes

- Insulin resistance
- Insufficient insulin secretion
- Increased hepatic gluconeogenesis
- Glucagon hypersecretion
- Defects in the secretion and action of incretin hormones

DeFronzo. *Med Clin North Am.* 2004;88:787–835, ix.

Type 2 diabetes mellitus is associated with a number of physiologic defects.

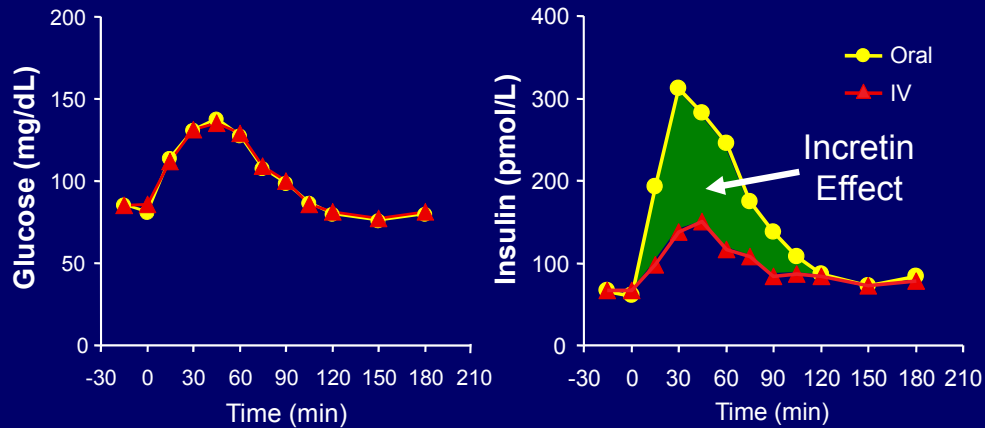
Obesity leads to insulin resistance, which is the classic pathophysiologic hallmark of the disease. In insulin resistance, the cells of the liver, muscle, and fat do not respond appropriately to insulin stimulation, the cells remain impermeable to glucose, glucose becomes trapped in the serum, and hyperglycemia results.

Although obesity causes insulin resistance, not all obese people have type 2 diabetes. We know that the pathophysiology of the disease is not limited to insulin resistance. Insufficient insulin secretion by the pancreas is also part of the problem. Early in the disease process, the pancreas produces enough insulin and amylin to overcome insulin resistance and signal the brain for satiety, respectively, thereby maintaining blood glucose levels. At this stage, the pancreas can meet the demands of the body, insulin levels are elevated relative to patients with normal insulin tolerance, and euglycemia (normal blood glucose level) is maintained. However, after years (often 5–10 years) of prolonged demand for elevated insulin production, beta-cell function begins to diminish. This phenomenon is commonly called “beta-cell failure.” Beta-cell failure results in insufficient insulin secretion. We start to observe elevated blood glucose levels at this point in the disease process.

Insulin is not the only hormone that controls blood glucose or that is part of the pathophysiology of type 2 diabetes. Glucagon, which we commonly know as the rescue hormone that is secreted from the alpha-cells of the pancreas in hypoglycemia, is inappropriately elevated after meals in patients with type 2 diabetes. The incretin hormones are secreted in the gastrointestinal tract and are also affected in type 2 diabetes.

The Incretin Effect: Insulin Secretion Is Greater in Response to Oral vs IV Glucose

Effects in healthy volunteers



IV = intravenous.

Nauck et al. *J Clin Endocrinol Metab.* 1986;63:492–498.

This slide depicts the “incretin effect.” In the graph on the left, the yellow line represents serum glucose levels following oral ingestion of glucose and the red line represents glucose levels following intravenous infusion of equal quantities of glucose to healthy volunteers. As shown in this graph, subjects had similar blood glucose levels irrespective of the route of administration.

The graph on the right shows the levels of secreted insulin in subjects who received glucose by the oral route (yellow line) or the intravenous route (red line). Considerably more insulin was secreted when glucose was administered by the oral route. The difference in the amount of insulin secreted following oral and intravenous administration of equivalent amounts of glucose is called the “incretin effect,” because the markedly greater secretion of insulin following oral administration results from the actions of incretin hormones.

Further research has shown that approximately 60% of postprandial insulin secretion is due to the effects of incretins.

The discovery that the incretin effect is diminished in patients with prediabetes and type 2 diabetes suggested that this deficit might be a target for pharmacologic intervention.

Properties of Incretin Hormones

- Released from gastrointestinal tract during ingestion of various types of foods
- Stimulate insulin secretion only when blood glucose levels are elevated
- Have glucose-dependent insulintropic effects

Creutzfeldt. *Diabetologia*. 1979;16:75–85.

Incretins are hormones released from the gastrointestinal tract in response to the intake of various types of food.

However, elevated incretin blood levels stimulate insulin secretion only in the presence of elevated blood glucose levels (when insulin is needed). Thus, the insulintropic effects of the incretin hormones are glucose dependent.

Incretin Hormones: GLP-1 and GIP

Glucagon-Like Peptide-1 (GLP-1)

- Is released from small and large intestine
- Increases glucose-dependent insulin secretion
- Slows gastric emptying
- Reduces food intake and body weight
- Suppresses glucagon secretion during hyperglycemia

Glucose-Dependent Insulinotropic Polypeptide (GIP)

- Is released from small intestine
- Increases glucose-dependent insulin secretion
- Has minimal effects on gastric emptying
- Has no significant effects on satiety or body weight
- Does not appear to inhibit glucagon secretion

Drucker. *Diabetes*. 1998;47:159–169. Drucker et al. *Lancet*. 2006;368:1696–1705.

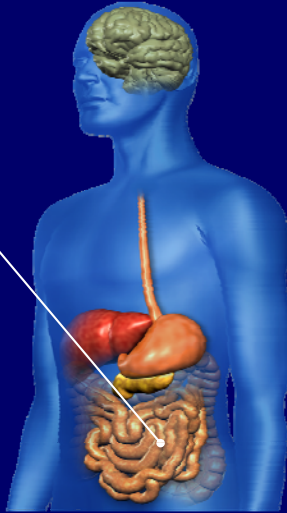
The 2 major incretin hormones are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).

GLP-1 and GIP share important similarities and also have several key differences. In response to food ingestion, both are secreted by the small intestine, although GLP-1 is also secreted by the large intestine. Both incretins stimulate glucose-dependent insulin secretion; however, GLP-1 also has beneficial effects on gastric emptying, body weight, and glucagon secretion that have not been observed with GIP.

Because of its multiple effects, GLP-1 has become an important target for the pharmacologic treatment of type 2 diabetes.

GLP-1 Exerts a Number of Beneficial Effects

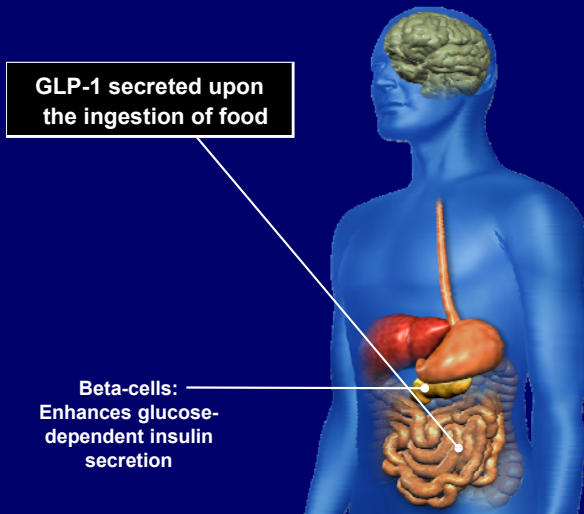
GLP-1 secreted upon the ingestion of food



Adapted from: Drucker. *Diabetes*. 1998;47:159-169.

Aside from its glucose-lowering properties, GLP-1 also has a number of beneficial effects that help to correct some of the pathophysiologic defects associated with type 2 diabetes. These include:

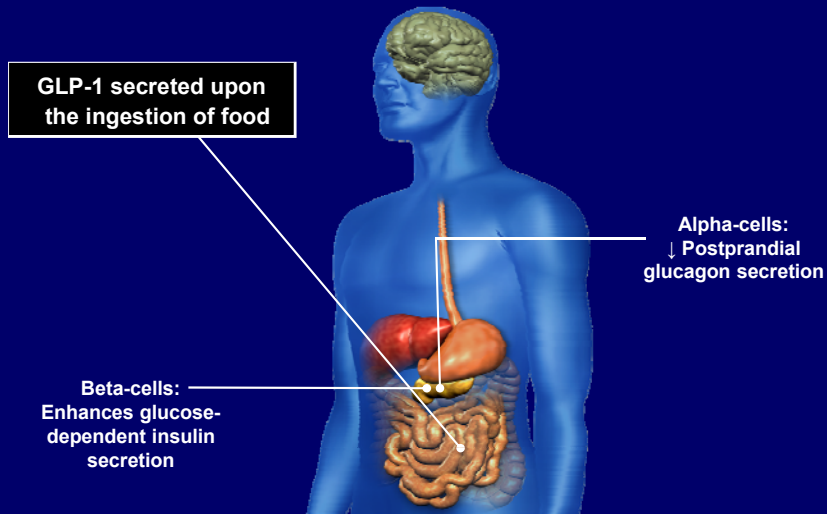
GLP-1 Exerts a Number of Beneficial Effects



Adapted from: Drucker. *Diabetes*. 1998;47:159-169.

- Promotion of insulin secretion in a glucose-dependent fashion

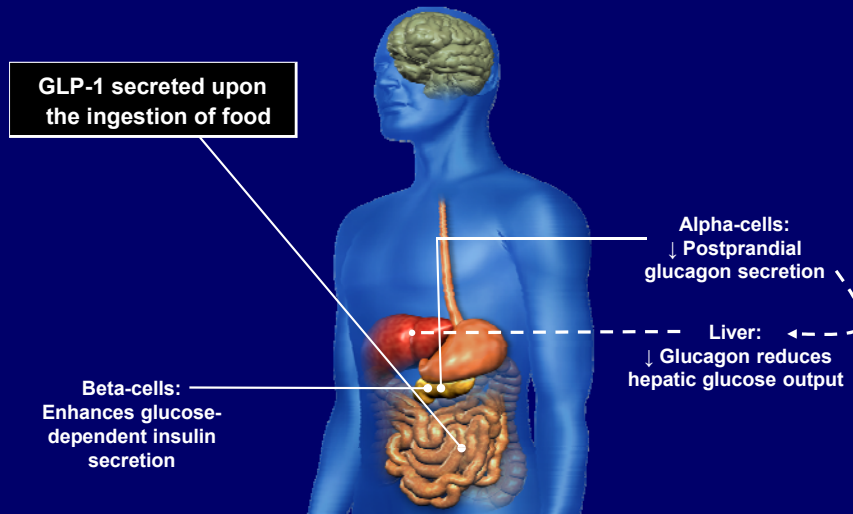
GLP-1 Exerts a Number of Beneficial Effects



Adapted from: Drucker. *Diabetes*. 1998;47:159–169.

- Reduction of postprandial glucagon secretion from pancreatic alpha-cells, which helps to maintain the counterregulatory balance between insulin and glucagon

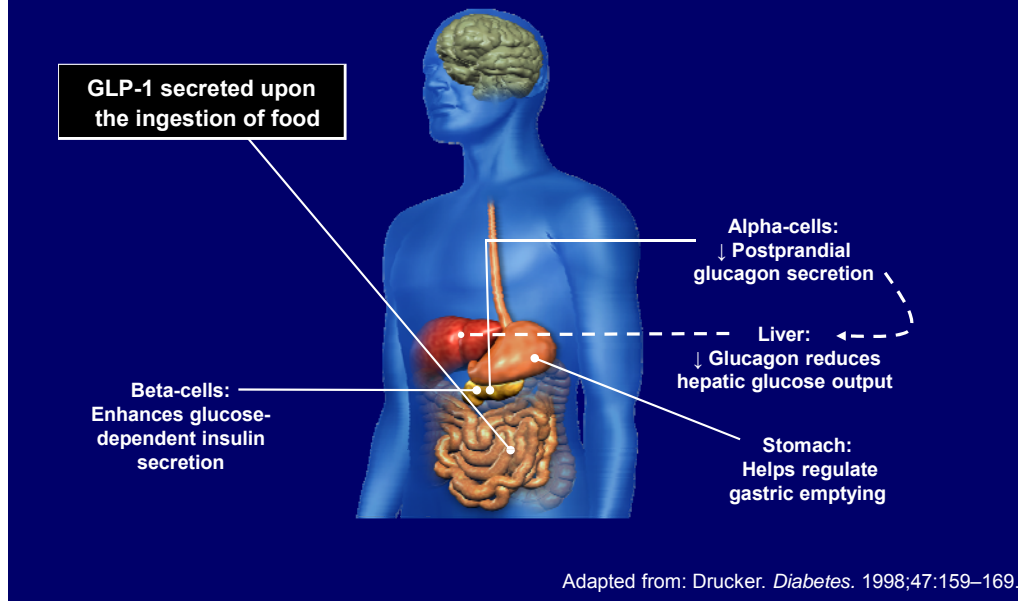
GLP-1 Exerts a Number of Beneficial Effects



Adapted from: Drucker. *Diabetes*. 1998;47:159–169.

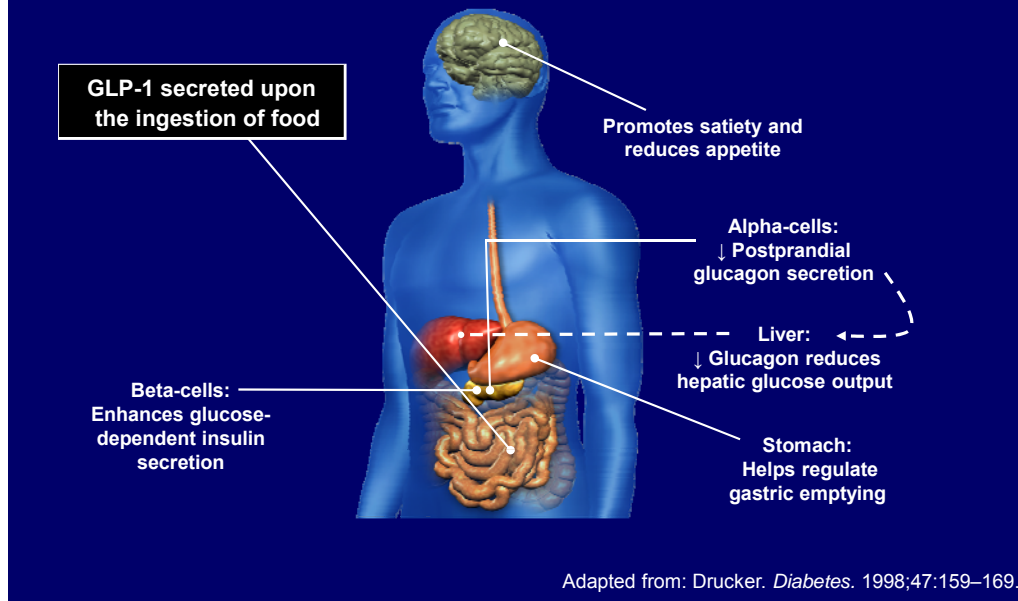
- Reduction of postprandial glucagon secretion

GLP-1 Exerts a Number of Beneficial Effects



- Regulation of the rate of gastric emptying such that meal nutrients are delivered to the small intestine and, in turn, absorbed more smoothly into the circulation, reducing peak nutrient absorption and insulin demand

GLP-1 Exerts a Number of Beneficial Effects



- Reduction of food intake because of increased satiety, which may, in turn, lead to weight loss
- GLP-1 also has an indirect benefit on beta-cell workload, since decreased glucagon secretion results in decreased postprandial hepatic glucose output.

Strategies for Enhancing GLP-1

- GLP-1 agonists (analogs)
 - Exogenous GLP-1
 - Resist degradation by DPP-4
 - Include exenatide, liraglutide, and exenatide long-acting release (LAR)
- DPP-4 inhibitors
 - Increase endogenous GLP-1 levels by blocking DPP-4
 - Include sitagliptin, saxagliptin, vildagliptin, and alogliptin

Drucker et al. *Lancet*. 2006;368:1696–1705.

GLP-1 would be an ideal agent for the treatment of type 2 diabetes because of its many beneficial effects. However, GLP-1 is not suited for chronic administration because it has a 2-minute half-life. The enzyme primarily responsible for GLP-1 breakdown is DPP-4.

Two pharmacologic approaches have been developed to prevent GLP-1 degradation by DPP-4: administration of GLP-1 agonists (also called GLP-1 analogs), which resist DPP-4 degradation; and administration of DPP-4 inhibitors, which block the DPP-4 enzyme.

Among the GLP-1 agonists, exenatide is currently approved for use in the United States, liraglutide is undergoing US Food and Drug Administration (FDA) review, and exenatide long-acting release (LAR) is in late-stage clinical development.

Among the DPP-4 inhibitors, sitagliptin and saxagliptin are currently approved for use in the United States and vildagliptin and alogliptin are in late-stage clinical development.

Each of these agents will be discussed in further detail.

Properties of Incretin-Based Therapies

Parameter	DPP-4 Inhibitors	GLP-1 Agonists
Administration	Oral	Subcutaneous injection
GLP-1 concentration	Close to physiologic (~2–3 ×)	Pharmacologic (>5 ×)
A1C reduction	–0.5% to –1.1%	–0.7% to –1.9%
Weight change	±0 kg	–3 to –5 kg
Beta-cell mass effects (animal studies)	Yes	Yes

Adapted from: Nauck et al. *Pharmacotherapy of Diabetes: New Developments*. 2007.
 Drucker et al. *Lancet*. 2008;372:1240–1250.
 Moretto et al. *Clin Ther*. 2008;30:1448–1460.
 A1C = glycosylated hemoglobin.

Although both DPP-4 inhibitors and GLP-1 agonists exploit the benefits of native GLP-1, they have several key differences. DPP-4 inhibitors are administered orally, whereas GLP-1 agonists are administered by subcutaneous injection.

Also, DPP-4 inhibitors enhance the effects of endogenous GLP-1, whereas GLP-1 agonists are an exogenous form of GLP-1.

GLP-1 concentrations are increased about 2 to 3 times above physiologic levels with DPP-4 inhibitors and more than 5 times above physiologic levels with GLP-1 agonists. Likely due to the higher GLP-1 levels achieved, GLP-1 agonists have a greater glycosylated hemoglobin (A1C)-reducing effect than DPP-4 inhibitors.

DPP-4 inhibitors are generally weight neutral and GLP-1 agonists are associated with weight loss. The potential for weight reduction is an attractive feature of the GLP-1 agonists, since more than 80% of patients with type 2 diabetes are overweight.

Studies in animals have shown that both GLP-1 agonists and DPP-4 inhibitors improve beta-cell function.

Checkpoint

Which of the following is NOT a property of GLP-1?

- a. It increases glucose-dependent insulin secretion
- b. It increases glucose-dependent glucagon secretion following meals
- c. It promotes satiety
- d. It delays gastric emptying

Now it's time for a checkpoint.

Which of the following is NOT a property of GLP-1?

- a. It increases glucose-dependent insulin secretion
- b. It increases glucose-dependent glucagon secretion following meals
- c. It promotes satiety
- d. It delays gastric emptying

Checkpoint Answer

The correct answer is b.

GLP-1 does not **increase** glucagon secretion after meals. It **suppresses** glucagon secretion after meals.

The correct answer is b.

GLP-1 does not increase glucagon secretion after meals. It suppresses glucagon secretion after meals.

DPP-4 Inhibitors

- FDA-approved: sitagliptin, saxagliptin
- Investigational: vildagliptin, alogliptin
- Mechanism of action: increase the half-life of endogenous GLP-1 by blocking degradation by DPP-4
- Beneficial effects
 - Increase glucose-dependent insulin release
 - Decrease postprandial glucagon

Drucker. *Lancet*. 2006;368:1696–1705.

One DPP-4 inhibitor, sitagliptin, is currently marketed in the United States. It is approved for monotherapy and combination therapy in adults with type 2 diabetes. Sitagliptin has not been studied in combination with insulin and, therefore, should not be administered with it.

In August 2009, saxagliptin was approved by the FDA. Currently, alogliptin and vildagliptin are investigational agents in the United States, although vildagliptin is available in other countries.

Since DPP-4 inhibitors increase the half-life of GLP-1, they have the same actions as those that increase endogenous GLP-1. They increase glucose-dependent insulin release, slow gastric emptying, decrease postprandial glucagon, and increase satiety.

Clinical Effects of DPP-4 Inhibitors

- In meta-analysis of 16 studies
 - DPP-4 inhibitors lowered A1C vs placebo (weighted mean difference, -0.74%)
 - Similar effects observed when DPP-4 inhibitor was administered as monotherapy or as add-on therapy
- In meta-analysis of 15 studies
 - FPG was reduced with DPP-4 inhibitors vs placebo (weighted mean difference, -18 mg/dL)

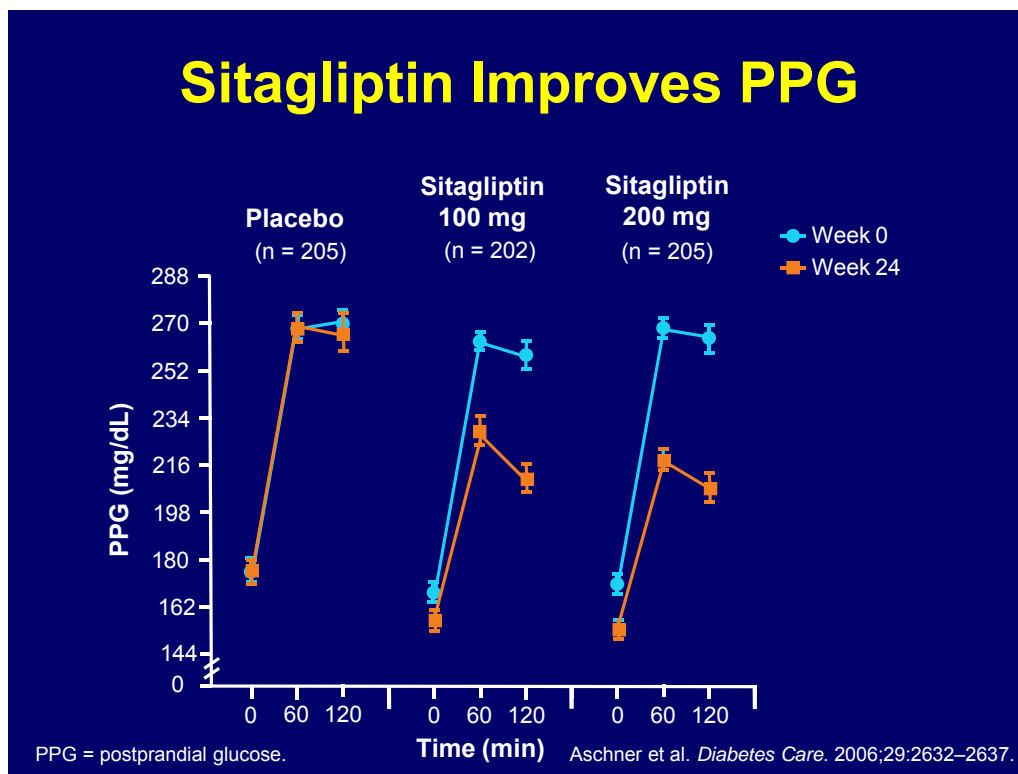
FPG = fasting plasma glucose.

Amori et al. *JAMA*. 2007;298:194–206.

A meta-analysis of 16 trials showed that therapy with the DPP-4 inhibitors sitagliptin and vildagliptin reduced weighted mean A1C by 0.74%. This effect was similar when the agents were used as monotherapy or added to existing treatment.

A meta-analysis of 15 trials showed that treatment with sitagliptin or vildagliptin also reduced weighted mean fasting plasma glucose (FPG), an important measure of diabetes treatment response, by 18 mg/dL. Although gliptins primarily lower the post-prandial glucose level, they do have a residual effect on fasting levels as well.

Sitagliptin Improves PPG



The effects of sitagliptin on postprandial plasma glucose (PPG) levels were studied in a randomized, double-blind, placebo-controlled study in which patients received sitagliptin 100 mg, sitagliptin 200 mg, or placebo for 24 weeks.

As shown on the slide, the reduction in 2-hour PPG from baseline at week 24 was significantly greater with sitagliptin 100 mg (–48.9 mg/dL) and 200 mg (–56.3 mg/dL) than with placebo (–2.2 mg/dL).

Saxagliptin and Alogliptin Improve Glycemic Control

- Saxagliptin monotherapy
 - Reduces A1C by 0.62% to 0.73%
- Alogliptin
 - Monotherapy
 - Reduces A1C by 0.56% to 0.59%
 - In combination with sulfonylurea, metformin, insulin, or pioglitazone
 - Reduces A1C by 0.38% to 0.8%

Pratley et al. *Diabetes*. 2008;57(Suppl 1):478-P.
Pratley et al. *Diabetes*. 2008;57(Suppl 1):445-P.
Nauck et al. *Diabetes*. 2008;57(Suppl 1):477-P.

Rosenstock et al. *Diabetes*. 2008;57(Suppl 1):517-P.
DeFronzo et al. *Diabetes*. 2008;57(Suppl 1):446-P.
Rosenstock et al. *Diabetes*. 2008;57(Suppl 1):444-P.

The efficacy of the 2 newer DPP-4 inhibitors, saxagliptin and alogliptin, is similar to that of sitagliptin and vildagliptin. Monotherapy with saxagliptin and alogliptin lower A1C by about 0.6% to 0.7%. Alogliptin has been studied in a 2-drug combination with a sulfonylurea, pioglitazone, insulin, and metformin, as well as in a 3-drug combination with metformin and pioglitazone, metformin and insulin, and pioglitazone and sulfonylurea. With these combinations, A1C reductions ranged between approximately 0.4% and 0.8%.

DPP-4 Inhibitors: Adverse Events

Adverse Events	No. of Studies	Risk Ratio DPP-4 vs Control	Mean % Experiencing Outcome	
			DPP-4	Control
Hypoglycemia	20	0.97	1.6	1.4
Nausea	10	0.89	2.7	3.1
Vomiting	6	0.69	1.3	1.5
Diarrhea	7	0.80	3.8	4.0
Abdominal pain	5	0.73	2.4	3.2
Cough	5	1.07	2.9	2.4
Influenza	6	0.87	4.1	4.7
Upper respiratory tract infection	9	0.99	6.3	6.4
Sinusitis	3	0.61	2.0	3.4
Urinary tract infection	5	1.52	3.2	2.4
Headache	13	1.38	5.1	3.9
Nasopharyngitis	12	1.17	6.4	6.1

Amori et al. *JAMA*. 2007;298:194–206.

The meta-analysis of DPP-4 inhibitors conducted by Amori et al showed that these agents have a relatively favorable safety and tolerability profile.

Since DPP-4 inhibitors increase insulin secretion only when glucose is present, the incidence of hypoglycemia is low. In contrast to the GLP-1 agonists, nausea was infrequently reported during clinical trials of DPP-4 inhibitor therapy. Urinary tract infection, headache, and nasopharyngitis were frequently reported adverse events (AEs), although the incidence of these events varied from study to study. When selecting patients who are likely to benefit from sitagliptin, it is advisable to avoid individuals with a history of recurrent urinary tract infection which is unrelated to type 2 diabetes or nasopharyngitis.

Hypoglycemia, although rare, is more commonly seen when sitagliptin is combined with a sulfonylurea than when it is given as monotherapy or in combination with agents other than a sulfonylurea. Therefore, clinicians should provide instructions to patients who will be taking sitagliptin together with a sulfonylurea. These include recognizing the signs and symptoms of hypoglycemia and how to prevent it.

Checkpoint

Monotherapy with a DPP-4 inhibitor results in A1C reductions of approximately 1.0% to 1.5%

- a. True
- b. False

And now another checkpoint.

Monotherapy with a DPP-4 inhibitor results in A1C reductions of approximately 1.0% to 1.5%.

- a. True
- b. False

Checkpoint Answer

False (b).

Monotherapy with a DPP-4 inhibitor results in A1C reductions of approximately 0.6% to 0.75%.

The correct answer is b, false.

Monotherapy with a DPP-4 inhibitor results in A1C reductions of approximately 0.6% to 0.75%.

Educating Patients About DPP-4 Inhibitors

- Oral administration (without regard to meals)
- Effects on blood glucose generally in 1–2 weeks
- Sitagliptin dose must be adjusted in patients with renal disease
- If prescribed in combination with sulfonylurea, review
 - Signs and symptoms of hypoglycemia
 - Treatment of hypoglycemia

Januvia™ (sitagliptin). Prescribing information. 2009.

Our current knowledge of DPP-4 inhibitor patient education comes from clinical use of sitagliptin. DPP-4 inhibitors can be administered orally without regard to meals.

Patients should be informed that they are likely to experience a reduction in their blood glucose levels within 1 to 2 weeks, although improvement may take longer in some patients.

Patients with a history of renal disease require sitagliptin dose adjustments.

When a DPP-4 inhibitor is being added to sulfonylurea therapy, the patient should be informed of the signs and symptoms of hypoglycemia and instructed on appropriate treatment as well as strategies to prevent hypoglycemic episodes.

Comparison of GLP-1 Agonists Available and in Development

Characteristic	Exenatide	Exenatide LAR	Liraglutide
Insulin secretion	↑	↑*	↑
Glucagon secretion	↓	↓*	↓
Fasting glucose	↓	↓↓↓	↓↓↓
Postprandial glucose excursions	↓↓↓	↓↓↓	↓↓↓
Weight reduction	Yes	Yes	Yes
Gastric emptying	↓	?	(↓)
Hypoglycemia [†]	No	No	No
Nausea	↑↑	↑	↑

*The active ingredient in exenatide LAR is identical to regular-release exenatide; no studies have reported the action profile of exenatide LAR with respect to insulin and glucagon secretion.

[†]Only if combined with other agents that can cause hypoglycemic episodes (eg, sulfonylureas).

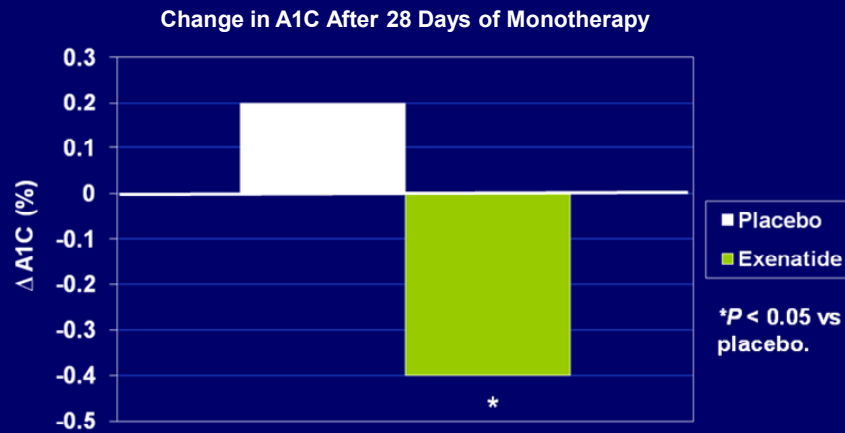
Adapted from: Nauck et al. *Pharmacotherapy of Diabetes: New Developments*. 2007.

Although the DPP-4 inhibitors have relatively similar profiles, the GLP-1 agonists have a number of important differences.

The longer-acting agents (liraglutide and exenatide LAR) tend to have greater effects on FPG than twice-daily exenatide. This results from their longer duration of action. The longer-acting agents also tend to be associated with less nausea compared with twice-daily exenatide.

Like the DPP-4 inhibitors, all of the GLP-1 agonists have a low risk for hypoglycemia due to the glucose-dependent nature of their effects.

Exenatide Monotherapy Improves Glycemic Control



N = 99.

Exenatide dose: 10 mcg twice daily.

Baseline A1C ranged from 7.5% to 8.0%.

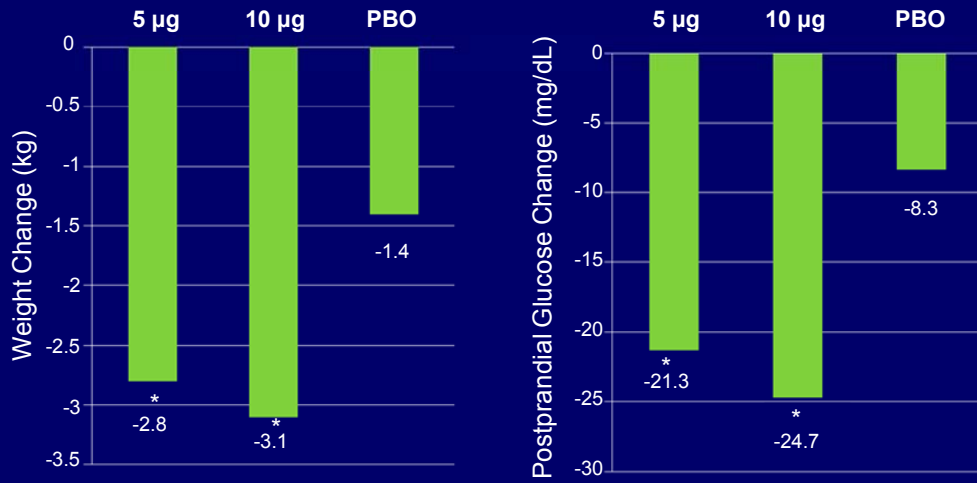
Nelson et al. *Diabetes Technol Ther.* 2007;9:317–326.

This graph shows the primary result of a monotherapy trial in which 99 patients with type 2 diabetes were randomized to receive exenatide 10 mcg or placebo, administered twice daily. Participants had relatively low baseline A1C values (ranging from 7.5% to 8.0%).

After 28 days of treatment, exenatide monotherapy was shown to significantly reduce A1C following 28 days of treatment. A1C was decreased by 0.4% compared with an increase of 0.2% with placebo. This difference was statistically significant ($P < 0.05$).

Exenatide Monotherapy Improves Weight and PPG vs Placebo

RCT, N=232 T2DM, Drug naïve, 24 wks



PBO = placebo; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus.

* $P < 0.001$.

Moretto et al. *Clin Ther.* 2008;30:1448–1460.

Moretto et al conducted a randomized, placebo-controlled 24-week monotherapy trial of exenatide (5 or 10 mcg twice daily) in 232 patients who had not previously received drug therapy for type 2 diabetes.

At end point, A1C reductions from baseline were -0.7% in the exenatide 5 mcg group, -0.9% in the exenatide 10 mcg group, and -0.2% in the placebo group. The differences between both exenatide groups and the placebo group were statistically significant.

As the slide shows, exenatide monotherapy resulted in statistically significant mean weight reductions from baseline of approximately 3 kg (6.6 lb) in both treatment groups over the study period.

Monotherapy with exenatide also improved PPG values from baseline, with mean reductions of approximately 21 to 25 mg/dL. These reductions were significantly greater than those observed with placebo.

Exenatide in Combination Therapy Improves Glycemic Control

Exenatide Added to	A1C Reduction ^{a,b}
Sulfonylurea	0.9%
Metformin	0.8%
Sulfonylurea + metformin	0.8%
Glitazone ± metformin	0.9%

^aFor 10 mcg dose.

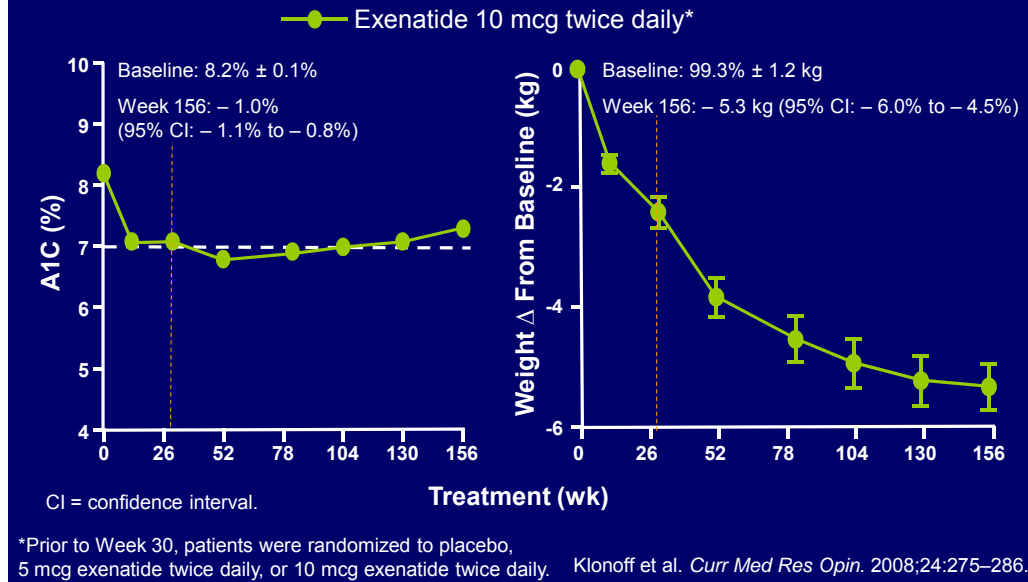
^b $P \leq 0.0001$.

Buse et al. *Diabetes Care*. 2004;27:2628–2635.
DeFronzo et al. *Diabetes Care*. 2005;28:1092–1100.
Kendall et al. *Diabetes Care*. 2005;28:1083–1091.
Zinman et al. *Ann Intern Med*. 2007; 30:477–485.

In addition to monotherapy, exenatide has also been studied in combination with a sulfonylurea, metformin, sulfonylurea + metformin combination, and a glitazone with or without metformin.

These randomized controlled trials demonstrated that the 10 mcg dose of exenatide reduces A1C by about 0.8% to 0.9%. As shown on the slide, A1C reductions were similar across studies.

Exenatide Improved A1C and Body Weight Over 3 Years



The effectiveness of older blood glucose–lowering agents such as sulfonylureas diminishes with time. Therefore, after a few years, A1C starts to increase despite continued therapy. However, some researchers suspect that GLP-1 agonists may have more durable effects because they preserve beta-cell function.

In an open-label study, the effect of exenatide was shown to be durable, both in terms of A1C and weight loss, over a period of 156 weeks (3 years). The graph on the left shows that mean A1C values declined rapidly at the beginning of exenatide treatment and then remained near the 7% goal for the remainder of the study.

The graph on the right shows that mean body weight continued to decrease over the 3 years of exenatide therapy.

It is important to note that this was not a controlled study and the analysis of A1C and weight-change data were reported only for patients who remained on therapy. Therefore, these results should be interpreted with caution until further studies are completed.

Exenatide Improves Cardiovascular Risk Factors Over 3.5 Years

Risk Factor	Change from Baseline (Mean ± SEM)
Total cholesterol (mg/dL)	-10.8 ± 3.1 ^a
LDL-C (mg/dL)	-11.8 ± 2.9 ^b
HDL-C (mg/dL)	8.5 ± 0.6 ^b
Triglycerides (mg/dL)	-44.4 ± 12.1 ^c
SBP (mm Hg)	-3.5 ± 1.2 ^d
DBP (mm Hg)	-3.3 ± 0.8 ^b

DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

^aP = 0.0007; ^bP < 0.0001; ^cP = 0.0003; ^dP = 0.0063

Klonoff et al. *Curr Med Res Opin.* 2008;24:275–286.

In December 2008, the FDA recommended that manufacturers who develop new therapies for patients with type 2 diabetes provide evidence that the therapy will not increase the risk of cardiovascular events. This recommendation applies to all agents that are currently being developed.

Data collected during a 3.5-year completer analysis and shown on this slide demonstrated that exenatide has beneficial effects on lipid levels and blood pressure. Outcome studies are needed to determine whether these effects translate into a reduced risk for cardiovascular events.

Checkpoint

Exenatide is effective in combination with a sulfonylurea and metformin.

- a. True
- b. False

It's time for another checkpoint.

Exenatide is effective combination with a sulfonylurea and metformin.

- a. True
- b. False

Checkpoint Answer

True (a).

Exenatide has been studied and found effective in various combinations, including triple combination with a sulfonylurea and metformin.

The correct answer is a, true.

Exenatide has been studied and found effective in various combinations, including triple combination with a sulfonylurea and metformin.

Adherence and Persistence More Favorable With Exenatide Than Insulin Glargine

Patient Characteristic	Exenatide	Insulin Glargine	<i>P</i>
For patients with >1 prescription fill, 12 mo MPR	68% ± 29%	58% ± 28%	<0.001
% With MPR ≥80%	47	29	<0.001
% Discontinuing treatment (refill gap >60 d)	56	75	<0.001
% Discontinuing treatment (refill gap >90 d)	34	52	<0.001

MPR = medication possession ratio, calculated as days of supply/365 days.

Fabunmi et al. *Curr Med Res Opin.* 2009 Feb 10.

Results of a recent study comparing exenatide with insulin glargine, another injectable medication, demonstrated that exenatide has a more favorable adherence rate. This may be due to the increased satiety and weight loss associated with GLP-1 agonists. (Medication possession ratio [MPR] is a formula used to determine adherence, measured from the first to the last prescription over a given time period.)

In this study, exenatide was associated with a greater MPR (in this case calculated as days of supply/365 days), a greater percentage of patients with an MPR greater than or equal to 80%, and fewer discontinuations (defined both as a 60-day and 90-day refill gap) versus insulin glargine.

The improved adherence rate observed with exenatide may result in improved treatment outcomes.

Managing GLP-1 Agonists Adverse Events

- Nausea
 - Usually transient
 - Maintain patient on lower dose until tolerated, then titrate up
 - Instruct patient to eat smaller meals
 - Instruct patient to administer within 60 minutes of meal
 - Not related to weight loss or efficacy
- Hypoglycemia
 - Rare but more likely if combined with a sulfonylurea
 - Give standard instructions for avoiding hypoglycemia
- Injection-site pain
 - Review injection technique
 - Change injection site with each dose

Nathan et al. *Diabetes Care*. 2009;32:193–203.
Byetta® (exenatide injection). Patient information. 2008.

Our knowledge of the AE profile of the GLP-1 agonists is based on clinical use of exenatide over several years.

Most of the AEs associated with the GLP-1 agonists involve the gastrointestinal system. They are usually mild and transient, although some patients are unable to tolerate the nausea that can accompany GLP-1 agonist therapy. To help them manage gastrointestinal effects, patients should be instructed to eat smaller, frequent meals and to administer treatment within 60 minutes of meals.

Overall, hypoglycemia is a rare AE, although it is more likely to occur when a GLP-1 agonist is administered in combination with a sulfonylurea. As previously mentioned, patients prescribed this combination should be aware of the signs of hypoglycemia and be given standard instructions for avoiding it.

Discomfort at the injection site can be minimized by proper injection technique and altering the site of the injection with each dose.

Exenatide and Pancreatitis Risk

- Acute pancreatitis 3 to 4 times greater in patients with type 2 diabetes
- Experience with exenatide:
 - October 2007 – FDA reports 30 cases of pancreatitis
 - August 2008 – FDA reports 6 cases of necrotizing or hemorrhagic pancreatitis
 - Report of 3-year clinical experience – No pancreatitis reported
- FDA recommendations:
 - Suspected pancreatitis: Promptly discontinue exenatide and other potentially suspect drugs
 - Confirmed pancreatitis: Initiate appropriate treatment; carefully monitor patient until recovery
 - Do not restart exenatide
 - Consider therapies other than exenatide in patients with a history of, or risk factors for, pancreatitis

US FDA. Drug Safety Newsletter. August 2008.
Klonoff et al. *Curr Med Res Opin.* 2008;24:275–286.

Some experts have noted that diabetes, irrespective of its treatment, is associated with a 3- to 4-fold increase in the risk of pancreatitis.

Recently, several postmarketing cases of acute pancreatitis in exenatide-treated patients have been reported to the FDA. In response to these reports, the FDA issued an update for health care providers on August 18, 2008. At the time of the update, 36 cases of exenatide-associated pancreatitis had been reported. These included 6 cases of hemorrhagic or necrotizing pancreatitis, 2 of which were fatal.

According to the FDA, exenatide should be discontinued if pancreatitis is suspected. If pancreatitis is confirmed, appropriate treatment should be initiated, and exenatide therapy should not be restarted. In patients with a history of pancreatitis, blood glucose-lowering agents other than exenatide should be considered.

Pancreatitis Symptoms

- Persistent severe abdominal pain
 - Can radiate to back
 - May be accompanied by nausea and vomiting
- Acute pancreatitis is confirmed by
 - Presence of elevated levels of serum amylase and/or serum lipase
 - Characteristic findings by radiological imaging

US FDA. Drug Safety Newsletter. August 2008.

In response to reports of exenatide-associated pancreatitis, the FDA has issued several recommendations.

Both health care providers and patients should be alert to the signs and symptoms of pancreatitis. Symptoms include persistent, severe abdominal pain that may radiate to the back. Pain may be accompanied by nausea and vomiting.

Acute pancreatitis can be confirmed by the presence of elevated levels of serum amylase and/or serum lipase. Its characteristic findings can be identified by radiological imaging.

If pancreatitis is confirmed, appropriate treatment should be initiated and the patient should be monitored closely until recovery is complete. Exenatide should not be restarted.

Educating Patients on GLP-1 Agonists

- Follow administration guidelines
 - Use disposable pen with detachable needle
 - Prime pen at first use only
- Store product appropriately
 - Keep between 36–46°F before opening
 - Keep between 36–77°F after opening
 - Do not store with needle on pen
 - Discard within 30 days of opening
- Be alert for signs and symptoms of pancreatitis

Byetta® (exenatide injection). Patient information. 2008.

Administration and storage guidelines for the GLP-1 agonists are currently available only for exenatide.

Health care providers should review the proper subcutaneous injection technique with their patients, because it differs from that of insulin. Additionally, patients should demonstrate the appropriate technique to verify their understanding and ability to use the device correctly. Exenatide is administered via disposable pen, which needs to be primed at first use only. The blood glucose-lowering effects of exenatide are apparent with the first dose.

Exenatide must be refrigerated prior to use. After it has been opened, the pen should not be exposed to temperatures below 36 degrees or above 77 degrees Fahrenheit. The needle should not be stored attached to the pen, and any remaining medication should be discarded within 30 days of opening.

Patients beginning exenatide should be instructed to contact their health care provider immediately if they experience severe and persistent abdominal pain, nausea, vomiting, and/or diarrhea.

Exenatide LAR Improves A1C and Reduces Weight Safely

- Randomized, open-label study (N = 303)
- At 30 weeks, compared with baseline, exenatide LAR
 - Reduced A1C by approximately 1.9%
 - Decreased FPG by approximately 42 mg/dL
 - Reduced weight by an average of 3.7 kg
- 77% of patients achieved goal of A1C $\leq 7\%$
- Low risk of hypoglycemia with both agents

Drucker et al. *Lancet*. 2008;372:1240–1250.

A newer formulation of exenatide, exenatide LAR, is now under clinical investigation for once-weekly administration.

When exenatide LAR was compared with twice-daily exenatide in a 30-week randomized, open-label study, the mean A1C reduction from baseline at study endpoint was approximately 1.9% with exenatide LAR and 1.5% with twice-daily exenatide. An A1C goal of $\leq 7\%$ was attained by 77% of the exenatide LAR group and 61% of the twice-daily exenatide group. The mean FPG reduction from baseline was 41.4 mg/dL with exenatide LAR and 25.2 mg/dL with twice-daily exenatide. Mean weight reduction from baseline was 3.7 kg with exenatide LAR and 3.6 kg with twice-daily exenatide.

The safety profile of exenatide LAR was similar to that of twice-daily exenatide. No major hypoglycemic episodes were reported in either group. In the exenatide LAR and twice-daily exenatide groups, respectively, the incidence of minor hypoglycemia was 14.5% and 15.4% in sulfonylurea-treated patients and 0% and 1.1% in patients who were not receiving concomitant sulfonylurea therapy.

Liraglutide Improves A1C As Monotherapy and in Combination

Concurrent Therapy	Study Groups	Max Mean Change, A1C (%)
None	Liraglutide 1.2 mg or 1.8 mg daily	-1.14
	Glimepiride 8 mg daily	-0.51
Glimepiride	Liraglutide, 0.6 mg, 1.2 mg, or 1.8 mg daily	-1.13
	Rosiglitazone 4 mg daily	-0.44
	Placebo	0.23
Metformin	Liraglutide 0.6 mg, 1.2 mg, or 1.8 mg daily	-1.0
	Glimepiride 4 mg daily	-1.0
	Placebo	0.1
Metformin + Rosiglitazone	Liraglutide 1.2 mg or 1.8 mg daily	-1.5
	Placebo	-0.5
Metformin + Glimepiride	Liraglutide 1.8 mg daily	-1.3
	Insulin glargine	-1.1
	Placebo	-0.24
Metformin ± Sulfonylurea	Liraglutide 1.8 mg daily	-1.12
	Exenatide 10 mcg bid	-0.79

Garber et al. *Lancet*. 2009;373:473-481.

Marre et al. *Diabet Med*. 2009;26:268-278.

Nauck et al. *Diabetes Care*. 2009;32:84-90.

Zinman et al. *Diabetes Care*. 2009 Mar 16.

Russell-Jones et al. *Diabetes*. 2008;57(Suppl 1):536-P.

Blonde et al. Can Diabetes Assoc Annual Meeting. 2008:P107.

Liraglutide, another long-acting GLP-1 agonist, is now under review by the FDA. Liraglutide is structurally different from exenatide or exenatide LAR. When studied as monotherapy, liraglutide resulted in significantly greater A1C reductions than glimepiride.

Liraglutide has also been studied in various combinations and compared with rosiglitazone, glimepiride, insulin glargine, and exenatide. Across these trials, it was shown that liraglutide lowers A1C by approximately 1% to 1.5%, a greater effect than seen with rosiglitazone and as effective as glimepiride. The effects of liraglutide on A1C were similar to those of insulin glargine when either agent was added to baseline metformin and glimepiride. Compared with exenatide, liraglutide resulted in a significantly greater A1C reduction. Administration of liraglutide also resulted in statistically significant weight loss across trials.

Checkpoint

Longer-acting GLP-1 agonists:

- a. Are less effective at lowering A1C than DPP-4 inhibitors
- b. Lower A1C by $\geq 1\%$
- c. Are weight neutral
- d. Are only effective when used with oral agents

And now it is time for another checkpoint.

Longer-acting GLP-1 agonists:

- a. Are less effective at lowering A1C than DPP-4 inhibitors
- b. Lower A1C by $\geq 1\%$
- c. Are weight neutral
- d. Are only effective when used with oral agents

Checkpoint Answer

The correct answer is b.

Studies show that longer-acting GLP-1 agonists lower A1C by about 1% to 1.9%.

The correct answer is b.

Studies show that longer-acting GLP-1 agonists lower A1C by about 1% to 1.9%.

Liraglutide Studies: Safety

- Nausea
 - Reported by 7.4% to 40% of patients
- Hypoglycemia
 - Reported in 2.8% to 12% of patients when sulfonylureas were **not** concomitant therapy
 - Reported in 9.2% to 27% of patients when sulfonylureas **were** concomitant therapy
- Maximum weight decrease
 - Ranged from 0.2 to 4.08 kg

Marre et al. *Diabet Med.* 2009;26:268–278.

Nauck et al. *Diabetes Care.* 2009;32:84–90.

Madsbad et al. *Diabetes Care.* 2004;27:1335–1342.

Garber A et al. *Lancet.* 2009;373:473–481.

Zinman et al. *Diabetes Care.* 2009 Mar 16.

Blonde et al. *CSEM/CDA Professional Conference.*

2008;29.

Russell-Jones et al. *Diabetes.* 2008;57 (Suppl 1):536-P.

As with other GLP-1 agonists, nausea was the most frequently reported AE with liraglutide. It was reported by 7.4% to 40% of patients and was generally transient and mild to moderate in intensity.

Hypoglycemia is a potential consequence of any blood glucose–lowering therapy, especially for any of the secretagogues, or agents that directly target the pancreas. Since GLP-1 agonists primarily target the gastrointestinal tract, the presence of glucose is required for GLP-1 to stimulate insulin release; therefore, a low incidence of hypoglycemia is expected with liraglutide therapy. In the clinical trials summarized here, minor hypoglycemia, typically defined as blood glucose values lower than 55 mg/dL and not requiring third-party assistance, was reported by 2.8% to 12% of liraglutide-treated subjects when a sulfonylurea was not given concomitantly. In studies in which liraglutide was given with a sulfonylurea, the incidence of minor hypoglycemia ranged between 9.2% and 27%. A total of 6 patients in 2 of the studies reported here experienced major hypoglycemia, defined as a blood glucose value that was below 55 mg/dL and required third-party assistance.

Like other GLP-1 agonists, liraglutide resulted in a greater weight reduction than active comparators (ie, rosiglitazone and glimepiride). Maximum reported weight loss with liraglutide ranged from 0.2 to 4.08 kg (about 0.5 to 9 pounds).

Improvement in Patient-Reported Outcomes With Liraglutide Monotherapy

- Decreases in BMI with liraglutide vs glimepiride resulted in:
 - Improved weight image
 - Less concern with weight
- Decreased weight concern was associated with improved:
 - Overall quality of life
 - General perceived health
 - Mental and emotional health

BMI = body mass index.

Bode et al. EASD 44th Annual Meeting 2008. Presentation 894.

Bode et al conducted a 52-week, randomized, double-dummy, placebo-controlled trial in which 746 patients received once-daily monotherapy with liraglutide 1.2 or 1.8 mg or glimepiride 8 mg. The study enrolled patients previously treated with lifestyle modification or oral monotherapy. A 77-item self-administered questionnaire assessed general perceived health, mental and emotional health, cognitive functioning, overall quality of life (QOL), weight image, weight concern, body size, and body distress.

At 52 weeks, reductions from baseline in A1C were greater with 1.2 mg liraglutide and 1.8 mg liraglutide than with glimepiride. Body mass index (BMI) increased significantly from baseline in the glimepiride group and decreased significantly in both liraglutide groups. Changes in both liraglutide groups differed significantly from those observed with glimepiride.

BMI reductions were associated with improvements in weight image and decreased weight concern. Decreased weight concern was associated with improvements in overall QOL, general perceived health, and mental and emotional health. The superior efficacy and positive impact of liraglutide 1.8 mg on weight and weight concern were associated with clinically important improvements in physical and emotional QOL domains.

Adverse Events With GLP-1 Agonists

Adverse Event	Number of Studies	Risk Ratio Incretin vs Control	Mean % Experiencing Outcome	
			GLP-1	Control
Nausea				
All GLP-1 vs comparator	9	2.92	32.9	12.6
Exenatide vs comparator	7	3.17	41.9	13.4
Liraglutide vs placebo	2	0.89	5.6	5.7
Vomiting				
All GLP-1 vs comparator	8	3.32	11.6	4.0
Exenatide vs comparator	6	3.52	14.1	4.0
Liraglutide vs comparator	2	0.62	2.3	3.6
Diarrhea				
All GLP-1 vs comparator	7	2.23	10.2	4.9
Exenatide vs comparator	6	2.27	11.0	4.9
Hypoglycemia				
Exenatide vs placebo	5	2.30	16.0	7.0
Exenatide vs insulin	2	1.02	2.3	2.3

Amori et al. *JAMA*. 2007;298:194–206.

Analysis of AEs associated with approved and investigational GLP-1 agonists shows that gastrointestinal events are the most frequently reported events.

Nausea, the most common AE, is thought to result from the feelings of satiety and delayed gastric emptying associated with GLP-1 agonist administration. GLP-1 agonist–related nausea is usually mild to moderate and generally dissipates over time. It can sometimes be managed by limiting meal sizes and administering the agent within 1 hour of beginning a meal.

As shown in the table, the risk of hypoglycemia is relatively low with the GLP-1 agonists. This finding differentiates these agents from many other diabetes therapies.

Checkpoint

Which of the following medications are associated with weight loss?

- a. Sulfonylureas – glyburide, glipizide, glimepiride
- b. DPP-4 inhibitors – sitagliptin, alogliptin, saxagliptin, vildagliptin
- c. GLP-1 agonists – exenatide, liraglutide, exenatide LAR
- d. Insulin

Time for our final checkpoint.

Which of the following medications are associated with weight loss?

- a. Sulfonylureas – glyburide, glipizide, glimepiride
- b. DPP-4 inhibitors – sitagliptin, alogliptin, saxagliptin, vildagliptin
- c. GLP-1 agonists – exenatide, liraglutide, exenatide LAR
- d. Insulin

Checkpoint Answer

The correct answer is c.

The GLP-1 agonists, including exenatide, liraglutide, and exenatide LAR, are all associated with weight loss.

DPP-4 inhibitors are weight neutral, and sulfonylureas and most types of insulin are associated with increases in weight.

The correct answer is c.

The GLP-1 agonists, including exenatide, liraglutide, and exenatide LAR, are all associated with weight loss.

DPP-4 inhibitors are weight neutral, and sulfonylureas and most types of insulin are associated with increases in weight.

Case Study - Zola

- 68-year-old female with type 2 diabetes for 8 years
- Comorbid conditions: hypertension, retinopathy
- BMI: 32 kg/m²
- Laboratory
 - Serum Creatinine = 1.2 mg/dL
 - Serum glutamic oxaloacetic transaminase (SGOT) = 25 unit/L
 - A1C = 8.1%
- Additional considerations:
 - Uncontrolled blood pressure
 - Social issues - husband died recently and patient is depressed
- Treatment history:
 - Previous sulfonylurea use with frequent episodes of hypoglycemia
 - Irregular blood glucose monitoring
 - Unsuccessful 3-month trial of diet and exercise
 - No history of pancreatitis
- Current diabetes medications: pioglitazone and metformin at optimal doses

Now let's look at a case.

Zola is a 68-year-old woman who has type 2 diabetes, is overweight, has uncontrolled hypertension, and has retinopathy, likely from her uncontrolled hypertension and diabetes. In addition, she is experiencing an episode of depression following the recent death of her husband.

She has a history of hypoglycemia with sulfonylurea therapy and does not monitor her blood glucose regularly. Although she is on optimal doses of pioglitazone and metformin, Zola needs to have her A1C reduced by at least 1.1%. She lives alone and thus needs to avoid hypoglycemia. In the next few slides, we will review the benefits and limitations of all of the therapeutic options available to treat Zola's hyperglycemia.

Adding Sulfonylurea

Benefits

- First-tier therapy per ADA/EASD algorithm
- Well-studied therapy with proven outcomes
- Inexpensive

Limitations

- Weight gain
- Hypoglycemia risk
- Does not preserve beta-cell function

EASD = European Association for the Study of Diabetes.

Nathan et al. *Diabetes Care*. 2009;32:193–203.

One option for Zola is to add sulfonylurea to her current diabetes medications (metformin and pioglitazone). According to the recently revised consensus algorithm developed by the ADA and the European Association for the Study of Diabetes (EASD), sulfonylurea is one of 2 classes of blood glucose–lowering options listed as a first-tier therapy, mainly because it is well studied and inexpensive. It has the potential to reduce her A1C to 7% or below, an appropriate target for Zola.

Limitations associated with sulfonylurea therapy include weight gain, hypoglycemia risk, and the inability to preserve beta-cell function.

Two relevant considerations are that Zola has a history of hypoglycemia with sulfonylurea therapy and she is currently overweight.

Adding Basal Insulin

Benefits

- Well established, with proven outcomes
- Relatively inexpensive depending upon type used
- First-tier therapy per ADA/EASD algorithm

Limitations

- Complicated, requires
 - Titration
 - Frequent monitoring
- Weight gain
- Injection – poor patient acceptance
- Hypoglycemia risk

Nathan et al. *Diabetes Care*. 2009;32:193–203.

Another option is to add basal insulin to Zola's existing regimen. This may be appropriate since she has had diabetes for at least 8 years and her beta-cell function may be diminishing. The ADA/EASD algorithm also classifies basal insulin as a first-tier therapy option because it is well established, is associated with proven outcomes, and is relatively inexpensive. Basal insulin may reduce Zola's A1C to below 7%.

However, basal insulin therapy does not appear to be the best approach for Zola. Even basal insulin regimens are relatively complex, and Zola is reluctant to use an injectable medication. Furthermore, insulin is associated with a risk of hypoglycemia. Because she experienced hypoglycemia during sulfonylurea therapy, Zola might also have hypoglycemic episodes during treatment with basal insulin, especially if she is not committed to monitoring her blood glucose regularly. Since Zola is obese, further weight gain is also a concern.

Switching to Intensive Insulin Therapy

Benefits

- Well-studied therapy with proven outcomes
- Marked A1C reduction

Limitations

- Complicated dose adjustments
- Frequent monitoring essential
- Poor patient acceptance
- Substantial patient education needed
- Weight gain likely
- Hypoglycemia risk

A third option for Zola is to switch to a regimen of intensive insulin therapy. Intensive insulin is well studied, with proven outcomes. It can reduce A1C substantially and thus is likely to lower Zola's A1C below 7%.

A major disadvantage of intensive insulin therapy is that, like basal insulin therapy, it can lead to hypoglycemia. Furthermore, intensive insulin therapy is a complex treatment regimen that requires substantial patient education. Zola is depressed due to the recent death of her husband, and this may not be an appropriate time to initiate a complex regimen. Additionally, Zola is overweight, so therapies that are weight neutral or associated with weight loss would be beneficial for her.

Adding a DPP-4 Inhibitor

Benefits

- Weight neutral
- Oral therapy
- Minimal hypoglycemia risk

Limitation

- Not first- or second-tier therapy per ADA/EASD algorithm

Nathan et al. *Diabetes Care*. 2009;32:193–203.

A fourth option is to add a DPP-4 inhibitor to Zola's current regimen. DPP-4 inhibitors are weight neutral, which is advantageous for an obese patient. They are administered orally and are associated with minimal risk for hypoglycemia, characteristics that are also desirable for Zola.

However, a DPP-4 inhibitor is less likely to reduce Zola's A1C below 7% than several other options, such as a sulfonylurea or intensive insulin therapy, and the ADA/EASD algorithm does not recommend DPP-4 inhibitors as first- or second-tier therapy.

Adding a GLP-1 Agonist

Benefits

- Weight loss
- May preserve beta-cell function
- Likely to reduce A1C to <7%
- Second-tier therapy per ADA/EASD algorithm (exenatide)
- Low risk of hypoglycemia

Limitations

- Injection
- Transient nausea

Nathan et al. *Diabetes Care*. 2009;32:193–203.

Adding a GLP-1 agonist is another option for Zola. Although GLP-1 agonists are administered by subcutaneous injection, dose titration is simpler than with insulin and the dose does not need to be adjusted for carbohydrate intake. Patient education is necessary because GLP-1 agonists can cause nausea, which is usually mild and transient.

A major advantage of the GLP-1 agonists is that they promote weight loss. The results of several clinical trials suggest that they may also preserve beta-cell function. A GLP-1 agonist can reduce Zola's A1C below 7%, and the ADA/EASD algorithm recommends exenatide, the only currently approved member of this class, as a second-tier therapy. Additionally, GLP-1 agonists have a low risk of hypoglycemia, a desirable characteristic for a patient with a history of this condition.

Given all of these considerations, a GLP-1 agonist would be a good choice for Zola.

Summary

- Incretin-based therapies help to address many challenges in the management of type 2 diabetes
- DPP-4 inhibitors
 - Enhance glucose-dependent insulin secretion
 - Enhance overall glycemic control by improving both fasting and postprandial hyperglycemia
 - Reduce A1C by about 0.74%
 - Are weight neutral

This activity has discussed the physiology of GLP-1, an incretin hormone, and the way in which incretin-based therapies can be used to treat type 2 diabetes.

Since DPP-4 rapidly degrades naturally occurring GLP-1, endogenous GLP-1 is not suitable for pharmacologic use.

DPP-4 inhibitors are orally administered agents that stimulate glucose-dependent insulin secretion, decrease postprandial and fasting glucose, lower A1C by 0.74%, and are weight neutral.

Summary (cont.)

- GLP-1 agonists
 - Increase glucose-dependent insulin secretion
 - Enhance overall glycemic control by improving both fasting and postprandial hyperglycemia
 - Reduce A1C by up to 1.9%
 - Promote weight loss
 - Exenatide included in ADA/EASD algorithm as second-tier therapy

Nathan et al. *Diabetes Care*. 2009;32:193–203.

GLP-1 agonists are DPP-4-resistant agents. Like DPP-4 inhibitors, GLP-1 agonists stimulate glucose-dependent insulin secretion and lower PPG and FPG.

They differ from DPP-4 inhibitors in that they have shown a greater A1C-lowering effect and cause weight loss.

Additionally, while the ADA/EASD algorithm does not currently recommend DPP-4 inhibitors as first- or second-tier therapy, exenatide, the only currently approved GLP-1 agonist, is a recommended second-line treatment option.