Incretin-Based Therapy: Evolving Treatment Strategies for Type 2 Diabetes

Supported by an educational grant from Novo Nordisk Inc.

Incretin-Based Therapy: Evolving Treatment Strategies for Type 2 Diabetes is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for nurses, dietitians, and pharmacists.
The following program is a taped presentation by Susan A. Cornell.

Susan A. Cornell is the assistant director of experiential education and an associate 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 over 24 years of practice in community pharmacy where she has practiced as a clinical pharmacist, diabetes educator and preceptor, as well as, the inaugural coordinator of the ADA recognized Dominick's Pharmacy Diabetes Self-Management Education program through 2004.

Dr. Cornell received her bachelor of pharmacy at the University of Illinois, College of Pharmacy and her Doctor of Pharmacy at Midwestern University.

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 numerous underserved community clinics.

Dr. Cornell recently completed her term as President of the Illinois Pharmacists Association in October 2011. She has received numerous awards and recognitions, including the 2010 Teacher of the Year Award, the 2010 American Association of Colleges of Pharmacy, Student Engaged Community Service Award, the 2008 American Association of Diabetes Educators Fellow Award, 2008 American Pharmacists Association Fellow award, the 2005 Midwestern University Golden Apple Teaching Award. She is an active member of the American Diabetes Association, 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 healthcare professionals and community groups and has published and contributed to many peer-reviewed, professional written and online publications.
After completing this activity, participants should be able to:

- Discuss evidence indicating that the management of US adults with type 2 diabetes needs improvement
- Explain the major characteristics and functions of endogenous incretin hormones and the mechanisms of action of the GLP-1 agonists and DPP-4 inhibitors
- Describe key data related to the safety, efficacy, and administration of the GLP-1 agonists and DPP-4 inhibitors in adults with type 2 diabetes
- Identify effective strategies for initiating and monitoring treatment with a GLP-1 agonist and a DPP-4 inhibitor in adults with type 2 diabetes
Glycemic control is essential for effective diabetes management. According to the 2012 joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), glycemic targets must be individualized. Nevertheless, the ADA considers an A1C of less than 7% to be a reasonable goal for many nonpregnant adults. This recommendation is based on the findings that lowering A1C to below or around 7% reduces microvascular complications of diabetes and is associated with long-term reduction in macrovascular disease if implemented soon after the diagnosis of diabetes.

However, as the graph shows, many US adults with diagnosed diabetes do not have an A1C of less than 7%. According to recent data from the National Health and Nutrition Examination Survey (NHANES), 47.5% of the overall population of adults with diabetes and 56.5% of Mexican Americans have an A1C of 7% or higher.

Clearly, glycemic control in many adults with diabetes needs to be improved.

Suboptimal glycemic control has many undesirable outcomes, including short-term complications that can reduce patients’ quality of life, increase their risk of death, and increase direct and indirect health care costs. Short-term complications that typically require hospitalization include diabetic ketoacidosis and hyperosmolar nonketotic coma.

The chart shows recent data compiled by the Agency for Healthcare Research and Quality that was presented in the National Healthcare Quality Report. The blue line shows that the overall rates of US hospital admissions for adults with short-term complications of diabetes increased between 2004 and 2008, from 55 to 61 per 100,000 people. (Note that data are not available for 2006.) The red line shows the achievable benchmark rates for the same period. These are the rates achieved by the 4 states with the lowest admission rate—Hawaii, Minnesota, Nebraska, and Utah. Between 2004 and 2008, the benchmark rate decreased from 40 to 38 per 100,000 people. Thus, the overall US population was moving away from the benchmark, again emphasizing the importance of achieving tighter glycemic control in people with diabetes.

Among the most important reasons for suboptimal glycemic control and undesirable outcomes in people with diabetes is nonadherence to the treatment regimen. Medication nonadherence is widespread in adults with type 2 diabetes, and nonadherence rates of at least 35% are often reported in clinical studies.\(^1\)-\(^4\) Nonadherence has many negative consequences, including higher A1C levels,\(^2\),\(^5\) increased risk for all-cause hospitalization,\(^5\) higher inpatient costs,\(^4\) and increased risk for all-cause mortality.\(^5\) Among the most common causes of nonadherence are complex medication regimens\(^1\),\(^3\) and concerns about hypoglycemia\(^3\) and weight gain.\(^3\),\(^6\)

Given the prevalence and negative consequences of nonadherence, adopting measures that may increase adherence is critical.


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**Nonadherence Contributes to Undesirable Outcomes**

- **Nonadherence**
  - A major reason for suboptimal glycemic control and undesirable outcomes
  - Rates of ≥35% often reported in people with type 2 diabetes\(^1\)-\(^4\)
  - Associated with higher A1C levels,\(^2\),\(^5\) increased risk for all-cause hospitalization,\(^5\) higher inpatient costs,\(^4\) and increased risk for all-cause mortality.\(^5\)
  - Often attributable to complex medication regimens\(^1\),\(^3\) and concerns about hypoglycemia\(^3\) and weight gain.\(^3\),\(^6\)

- **Adopting measures to increase adherence is critical**
THE RATIONALE FOR INCREDIN-BASED THERAPY
One conclusion suggested by the undesirable outcomes experienced by many adults with type 2 diabetes is that health care providers need to make optimal use of the various classes of glucose-lowering drugs that are now available. This activity focuses on the effective use of incretin-based therapies—glucagon-like peptide 1 receptor agonists (GLP-1 agonists) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)—in clinical practice.

The emergence of the GLP-1 agonists and the DPP-4 inhibitors as established classes of glucose-lowering agents is reflected in their changing positioning in recent joint position statements of the ADA and the EASD. In the 2009 statement, the GLP-1 agonist class—at that time represented only by exenatide twice daily (ExBID)—was included only as a tier 2 option, for patients for whom avoiding hypoglycemia and losing weight were especially important. The DPP-4 inhibitors were not included in the algorithm at all.

In contrast, both the GLP-1 agonists and the DPP-4 inhibitors occupy prominent positions in the general recommendations included in the 2012 joint statement. As shown in the diagram, both types of incretin-based therapy are recommended as components of 2-drug and 3-drug combinations. (Note that the left-to-right positioning of the various treatment options does not signify any specific preference.) In assessing the advantages of the GLP-1 agonists, the 2012 statement notes that they are not associated with hypoglycemia when given as monotherapy, they result in weight reduction, and the potential exists for improved beta-cell mass and/or function and for cardiovascular protective actions. The authors identify a lack of hypoglycemia when given as monotherapy and a good overall tolerability profile as advantages of the DPP-4 inhibitors.


Type 2 diabetes is a progressive metabolic disorder characterized by functional defects in several organs. Patients experience progressive pancreatic islet dysfunction, including qualitative and quantitative abnormalities in insulin secretion from beta cells and unrestrained glucagon secretion from alpha cells. They also have insulin resistance in muscle and adipose tissue, as well as dysregulated hepatic glucose production.

People with type 2 diabetes also exhibit qualitative and quantitative abnormalities in the secretion of amylin. Amylin, which is co-secreted with insulin from pancreatic beta cells, works together with insulin to suppress glucagon secretion. It also helps to regulate gastric emptying, thereby influencing the rate at which glucose enters the blood.

Type 2 diabetes is also characterized by impaired incretin hormone activity. (Note that the word “incretin” is an acronym for INtestinal seCRETion of INsulin.) The incretin hormones are discussed in the next slides.

The incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) are produced by specialized endocrine cells, called enteroendocrine cells, in the gastrointestinal (GI) tract.¹ Incretin hormones are secreted in response to the entry of nutrients into the gut.¹ GLP-1 secretion is stimulated by glucose, amino acids, and fat, and GIP secretion is stimulated by fat and, to a lesser extent, glucose.¹ The incretin hormones increase insulin secretion from pancreatic beta cells in a glucose-dependent manner.¹ Studies conducted in human volunteers during the 1960s showed that oral ingestion of glucose led to a greater insulin response than intravenous (IV) administration of an equivalent amount of glucose.² This phenomenon, called “the incretin effect,”¹ is discussed further on the next slide.

GLP-1 also has other effects. It slows gastric emptying, suppresses postprandial glucagon secretion from pancreatic alpha cells, and promotes satiety and reduces appetite, thereby lowering food intake and body weight.³

Preclinical studies have shown that both GLP-1 and GIP reduce beta-cell apoptosis (cell death) and promote beta-cell proliferation,⁴ although these effects have not been demonstrated in humans.

As just mentioned, the incretin effect is the phenomenon by which oral ingestion of glucose provokes a greater insulin response than IV administration of the same amount of glucose. The term derives from the fact that the increased secretion of insulin following oral glucose administration is primarily due to the actions of incretin hormones GLP-1 and GIP.

This slide depicts the incretin effect, presenting data for human volunteers who did not have diabetes. In the graph on the left, the yellow line represents mean serum glucose levels following oral ingestion of glucose and the red line represents mean glucose levels following IV infusion of an equivalent amount of glucose. The superimposition of the lines shows that subjects had similar serum glucose levels regardless of the route of administration.

The graph on the right shows mean levels of secreted insulin when subjects received glucose by the oral route (yellow line) or the IV route (red line). As the graph shows, considerably more insulin was secreted when glucose was administered by the oral route. Additional research has shown that average insulin responses to IV glucose infusion are 30% to 70% less than average insulin responses to oral glucose ingestion. Studies have also shown that the insulinotropic effects of GLP-1 and GIP are additive to each other.

The incretin effect is impaired in people with type 2 diabetes, resulting in defective glucose-stimulated insulin secretion, reduced glucose clearance, increased glucagon levels, and quicker gastric emptying. The mechanisms underlying this defect are incompletely understood and have generated considerable controversy. The views summarized here are those of Dr. Michael Nauck, MD, PhD.

Most, but not all, studies have found that the secretion of GIP and GLP-1 is not reduced in people with type 2 diabetes. However, the insulinotropic activity of GIP is greatly compromised, perhaps due to decreased beta-cell mass and reduced maximum insulin secretory capacity of the beta cell. GLP-1 retains its activity but, at physiologic levels, cannot compensate for compromised GIP activity.

Although GLP-1 retains its activity in people with type 2 diabetes, at physiologic levels it cannot compensate for the greatly reduced activity of GIP. However, as we will discuss, supraphysiologic levels of GLP-1 can partially compensate for impaired GIP activity.

The foundation of today's incretin-based therapy is the finding that infusion of native GLP-1 to patients with type 2 diabetes\(^1\)
- Normalized beta-cell responsiveness to glucose
- Improved the insulin response to glucose
- Reduced daytime plasma glucose levels to near normal

Large-scale, long-term administration of native GLP-1 is not feasible, because it is rapidly degraded by DPP-4, a ubiquitous enzyme\(^1\)

Researchers focused on two therapeutic approaches
- GLP-1 agonists: replicate the activities of native GLP-1 but are less susceptible to DPP-4 degradation\(^1\)
- DPP-4 inhibitors: limit degradation of endogenous GLP-1, prolonging GLP-1 availability\(^1,2\)

The foundation of today's incretin-based therapy is the finding that infusion of native GLP-1 to volunteers with type 2 diabetes normalized beta-cell responsiveness to glucose, improved the insulin response to glucose, and reduced daytime plasma glucose to near-normal levels.\(^1\)

Despite these benefits, large-scale, long-term administration of native GLP-1 is not feasible, because it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme.\(^1\)

Therefore, researchers focused on two therapeutic approaches. The first was the development of GLP-1 agonists, which replicate the activities of native GLP-1 but are less susceptible to DPP-4 degradation.\(^1\) The second was the development of DPP-4 inhibitors, which limit the degradation of endogenous GLP-1, thereby prolonging GLP-1 availability.\(^1,2\)

This slide shows that the GLP-1 agonists and the DPP-4 inhibitors have many of the same effects, but that the effects of the DPP-4 inhibitors are generally less potent. Although both classes of drugs increase beta-cell mass and proliferation, reduce beta-cell apoptosis, enhance glucose-dependent insulin secretion, reduce hepatic glucose production, and improve fasting and postprandial glucose levels, these effects are usually pronounced with the GLP-1 agonists and modest with the DPP-4 inhibitors.

These 2 classes of drugs also differ in several important respects. The GLP-1 agonists delay gastric emptying, increase satiety, and reduce food intake, whereas the DPP-4 inhibitors have negligible effects in these areas. The GLP-1 agonists promote weight loss, whereas the DPP-4 inhibitors are weight neutral.

Another important difference between these classes of incretin-based therapy is that GLP-1 agonists are administered by subcutaneous injection, while DPP-4 inhibitors are administered orally.

Throughout the rest of this activity, we will be reporting data from phase 3 clinical trials of incretin-based therapies. Both the GLP-1 agonists and the DPP-4 inhibitors are relatively new classes of glucose-lowering agents that have been evaluated rigorously in large, complex clinical trial programs.

Data have been intensively analyzed to highlight differences from comparators.

Published values for the same parameter often differ (eg, because data for different subpopulations are being reported).

All data sources are identified in this activity.

Note About Clinical Data for Incretin-Based Therapies

- GLP-1 agonists and DPP-4 inhibitors are relatively new classes of glucose-lowering agents that have been evaluated rigorously in large, complex clinical trial programs.
- Data have been intensively analyzed to highlight differences from comparators.
- Published values for the same parameter often differ (e.g., because data for different subpopulations are being reported).
- All data sources are identified in this activity.

Throughout the rest of this activity, we will be reporting data from phase 3 clinical trials of incretin-based therapies. Both the GLP-1 agonists and the DPP-4 inhibitors are relatively new classes of glucose-lowering agents. Clinical data for members of both classes have been intensively analyzed to highlight differences from comparators. In many cases, these differences are small. Published values for the same parameter of the same study often differ. For example, different publications may report different values for the mean change from baseline in the A1C level. There are many reasons for these differences, but they often occur because data for slightly different populations are being reported.

In this activity we have used footnotes to identify the sources of all data reported. We have reported data presented in the current prescribing information for each agent unless there was a compelling reason to use a different source.
A low incidence of hypoglycemia is a principal advantage of incretin-based therapy. Hypoglycemia has been classified differently in different clinical trial programs (and sometimes within the same program). Whenever possible in this activity, we have reported data for the incidence of “minor” and “major” hypoglycemia. Minor hypoglycemia refers to an episode that a patient could self-treat. Major hypoglycemia refers to an episode requiring assistance from another person (layperson or health care provider).
The accurate statement is: ___________.

a. less than one-quarter of US adults with diagnosed diabetes have an A1C of ≥7%

b. GLP-1 and GIP are released from the GI tract during the ingestion of food

c. the incretin effect remains intact in people with type 2 diabetes

d. both the GLP-1 agonists and the DPP-4 inhibitors markedly increase satiety
The correct answer is b.

GIP and GLP-1 are released from the GI tract during the ingestion of food.
GLP-1 AGONISTS
The table shows the 3 GLP-1 agonists that were approved for use in the US as of March 2013. Exenatide twice daily (ExBID) has the brand name Byetta®. It is marketed by Amylin Pharmaceuticals, Inc., and was approved by the US Food and Drug Administration (FDA) on April 28, 2005. Liraglutide, marketed under the name Victoza®, is manufactured by Novo Nordisk Inc. It received FDA approval on January 25, 2010. Most of the trials in the phase 3 clinical trial plan were part of the Liraglutide Effect and Action in Diabetes (LEAD) program. Exenatide once weekly (ExQW) has the brand name Bydureon™ and is marketed by Amylin Pharmaceuticals, Inc. It received FDA approval on January 27, 2012. The name of the phase 3 program was “DURATION,” which is the acronym for Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly. Each of the approved GLP-1 agonists is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Other GLP-1 agonists are now under development. According to www.clinicaltrials.gov, the most advanced of these agents are albiglutide, dulaglutide, and lixisenatide. Investigational agents will not be discussed in this activity. However, lixisenatide, which has been approved for use in the member states of the European Union and several other countries, is briefly covered on the next slide.


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**Table: GLP-1 Agonists Approved for Use in the US**

<table>
<thead>
<tr>
<th>Agent (Brand Name)</th>
<th>Manufacturer</th>
<th>Major Development Program</th>
<th>FDA Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ExBID (Byetta®)†</td>
<td>Amylin†</td>
<td>—</td>
<td>April 28, 2005²</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)³</td>
<td>Novo Nordisk³</td>
<td>LEAD⁴</td>
<td>January 25, 2010²</td>
</tr>
<tr>
<td>ExQW (Bydureon™)⁵</td>
<td>Amylin⁵</td>
<td>DURATION⁶</td>
<td>January 27, 2012²</td>
</tr>
</tbody>
</table>

†Effective March 2013. According to www.clinicaltrials.gov, investigational GLP-1 agonists in late-stage development are albiglutide, dulaglutide, and lixisenatide. Lixisenatide, which is approved for use in the member states of the European Union and several other countries, is briefly covered on the next slide.

²Each agent is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

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ExBID = exenatide twice daily; DURATION = Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly; ExQW = exenatide once weekly; FDA = US Food and Drug Administration; LEAD = Liraglutide Effect and Action in Diabetes.
Lixisenatide is a GLP-1 agonist that has been approved for use in combination with oral glucose-lowering agents and basal insulin in the member states of the European Union (EU) and in several other countries.\(^1\)\(^2\) The proprietary name for lixisenatide in Europe is Lyxumia\(^\text{®}\).\(^2\) In February 2013, the FDA accepted a New Drug Application for lixisenatide.\(^2\)

Although it was not approved for use in the United States when this activity was finalized, US health care providers should have some knowledge of lixisenatide, since visitors to this country may be taking it. The standard maintenance dose is 20 μg, administered once daily.\(^3\)

In the phase 3 GetGoal program, lixisenatide showed efficacy in reducing plasma glucose and A1C levels, with a pronounced effect on postprandial plasma glucose (PPG).\(^4\) The potent effect of lixisenatide on PPG levels is thought to be due in part to its marked ability to delay gastric emptying.\(^4\)

This table shows that the GLP-1 agonists have different chemical and pharmacokinetic characteristics. Their varying time to maximum plasma concentration ($T_{\text{max}}$) and elimination half-life ($T_{1/2}$) values explain why the dosing intervals for these agents range from twice daily to once weekly. Note that 2 different $T_{\text{max}}$ values are reported for ExQW. Following a single dose of this agent, there is an initial period of release of surface-bound exenatide, followed by a gradual release of exenatide from microspheres, resulting in 2 subsequent exenatide plasma peaks in plasma—the first at around 2 weeks and the second between weeks 6 and 7. However, when ExQW is administered every 7 days, steady-state is achieved after 6 to 7 weeks, and pronounced drug-level fluctuations no longer occur.

Clinically significant drug interactions with the GLP-1 agonists are uncommon. However, since all GLP-1 agonists delay gastric emptying, they have the potential to impact the absorption of concomitantly administered oral medications. Therefore, caution should be exercised when oral medications are concomitantly administered with a GLP-1 agonist. Patients who are taking oral medications that depend on threshold concentrations for efficacy, such as contraceptives and antibiotics, should take them at least 1 hour before ExBID injection. This stipulation does not apply to ExQW or to liraglutide.

Because both ExBID and ExQW are primarily eliminated by the kidneys, neither should be used in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) or end-stage renal disease (ESRD). Both exenatide products should be used with caution in patients with a history of renal transplantation or moderate renal impairment (CrCl 30–50 mL/min). Hepatic impairment is not expected to affect blood concentrations of ExBID or ExQW, since exenatide is cleared primarily by the kidney. Unlike exenatide, liraglutide is endogenously metabolized and no specific organ serves as a major route of elimination. Liraglutide should be used with caution in patients with renal or hepatic impairment, but no dose adjustments are recommended for these patients.

The GLP-1 agonists are administered subcutaneously, in the abdomen, thigh, or upper arm.\textsuperscript{1–3} To reduce the incidence and severity of GI side effects, patients beginning treatment with ExBID should receive a 5 µg dose, given twice daily, for the first month.\textsuperscript{1} Based on clinical response, the dose can then be increased to 10 µg, twice daily, if warranted. ExBID can be administered at any time within the 60-minute period before the morning and evening meals, or before the 2 main meals of the day, approximately 6 hours or more apart. It should not be administered after a meal. A patient who is treated with both ExBID and insulin should never mix the 2 agents.

To enhance tolerability, liraglutide should be initiated with a dose of 0.6 mg per day for 1 week.\textsuperscript{2} After that, the dose should be increased to 1.2 mg. If warranted, the dose can be further increased to 1.8 mg. Liraglutide is administered once daily, at any time of day, independently of meals. When liraglutide is used with insulin, the 2 agents must be administered as separate injections. Liraglutide and insulin can be administered in the same body region (eg, right thigh), but the injections should not be adjacent to each other.

ExQW should be administered as a 2 mg dose, once every 7 days.\textsuperscript{3} The dose can be administered at any time of day, with or without meals. Prior treatment with ExBID is not required when initiating ExQW therapy. As of March 2013, the concurrent use of ExQW with insulin is not recommended. Patients should use a different injection site each week when injecting ExQW in the same region.

Both ExBID (Byetta®) and liraglutide (Victoza®) are administered with disposable pens that are similar to insulin pens. There are 2 different Byetta® pens, each dispensing 60 doses of ExBID. The pen used to administer 5 µg doses has a total capacity of 1.2 mL, and the pen used for 10 µg doses has a total capacity of 2.4 mL. The 5 µg pen has an orange and blue label and the 10 µg pen has a yellow and blue label. Both have dark blue caps. The Victoza® pen contains 3 mL of liraglutide and can be used to administer liraglutide doses of 0.6, 1.2, or 1.8 mg.

Both Byetta® and Victoza® pens use disposable, single-use pen needles that are not included with the pens. Needles of 29G through 31G can be used with Byetta® pens. Novo Nordisk recommends that a 30G or 32G NovoFine® or NovoTwist® pen needle be used with the Victoza® pen.

Instructions for storing, using, and disposing of Byetta® and Victoza® pens are similar to those for insulin pens. Byetta® and Victoza® pens must be prepared before they are used for the first time (or if dropped), but unlike insulin pens, they do not need to be primed before each use. The manufacturers’ websites have various print materials and videos to help patients learn to use these pens.
Since ExQW consists of microspheres, the extremely narrow-gauge needles used with pen-type devices would not be suitable for ExQW administration. Therefore, unlike ExBID and liraglutide, ExQW (Bydureon™) is administered with a syringe. ExQW is dispensed in a carton that includes 4 single-dose trays and an instruction manual.¹

As shown in the lower picture, each tray holds a vial containing powder for a single 2 mg dose of ExQW, a prefilled syringe containing 0.65 mL of diluent, a vial connector, and 2 needles (one of which is provided as a replacement).¹² The needles are 23G in diameter and 8 mm (5/16 inch) in length. ExQW must be injected immediately after the powder is suspended in the diluent and transferred to the syringe.³

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This slide shows mean A1C reductions from baseline in phase 3 clinical trials of GLP-1 agonists. Most of these studies lasted for 24 to 30 weeks, although the liraglutide monotherapy trial was a 52-week study. As shown in the table, mean A1C reductions ranged from 0.7% to 1.5% when a GLP-1 agonist was given as monotherapy, with the greatest reductions observed with liraglutide 1.8 mg and ExQW. According to the 2012 ADA–EASD position statement, the A1C reductions observed with GLP-1 agonist monotherapy compare favorably with those attained with other glucose-lowering drugs.

Reductions ranged from 0.5% to 1.5% when a GLP-1 agonist was given with 1 or 2 oral glucose-lowering drugs, and from 0.5% to 1.7% when a GLP-1 agonist was given with basal insulin. One of the most important recent developments in the treatment of type 2 diabetes was the FDA’s approval of the use of ExBID and liraglutide in combination with basal insulin. Note, however, that ExQW is not currently approved for use with basal insulin and that none of the GLP-1 agonists are currently approved for use with prandial insulin.

Using the A1C reduction data shown in this table to draw conclusions about the relative efficacy of the various GLP-1 agonists is not useful, due to differences in study populations, baseline A1C values, and methodologies. Data from studies in which two GLP-1 agonists were compared directly are discussed later in this activity.

This slide shows median changes in body weight from baseline to end point in phase 3 clinical trials of GLP-1 receptor agonists. These data demonstrate that promotion of weight reduction is an important characteristic of this therapeutic class. Overall, weight reduction was greatest when GLP-1 agonists were administered as monotherapy, with mean reductions ranging from 2.0 kg to 2.9 kg. However, weight loss also occurred when GLP-1 agonists were given as a component of double or triple therapy, with decreases ranging from 0.2 kg to 2.8 kg. There was a slight weight increase, of 0.3 kg, when liraglutide 1.2 mg was administered with a sulfonylurea.

Because many patients with type 2 diabetes are overweight and treatment with insulin, sulfonylureas, TZDs, and glinides often results in weight gain, the weight-reducing potential of the GLP-1 agonists is an especially beneficial characteristic. The 2012 ADA–EASD position statement describes weight loss as the main advantage of the GLP-1 agonists.

In addition to their effectiveness in reducing blood glucose levels and body weight, GLP-1 agonists have shown many beneficial effects on cardiovascular risk parameters. Data from studies in which these effects were investigated were recently reviewed by several experts.\(^1\)–\(^3\) In human laboratory studies, GLP-1 agonists promoted vasodilation, improved endothelial function, and increased sodium excretion.\(^1\) In clinical trials, they reduced BP, especially systolic BP (SBP), and this reduction appeared to be largely independent of weight loss.\(^1,2\) GLP-1 agonist therapy has also been shown to decrease triglyceride and free fatty acid levels.\(^1,2\) Improvements in several surrogate markers of cardiovascular disease risk were reported in clinical trials, with reduced levels of C-reactive protein, adiponectin, plasminogen activator inhibitor-1, and brain natriuretic peptide.\(^1,2\)

The only potentially harmful cardiovascular effect of GLP-1 therapy is a modest increase in heart rate.\(^3\) Increases of up to 4 beats per minute have often been reported in clinical trials.\(^3\) The clinical significance of this effect is not currently known.\(^3\)

The effects of GLP-1 therapy on cardiovascular parameters are now undergoing further investigation in many clinical studies.\(^1\)

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Prescribing information for ExBID, liraglutide, and ExQW includes the disclaimer that there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with a specific GLP-1 agonist or any other glucose-lowering drug.¹⁻³

Nevertheless, data from a retrospective study suggest that treatment with a GLP-1 agonist might reduce the risk of cardiovascular disease (CVD) events.⁴ The investigators analyzed pharmaceutical insurance claims in the LifeLink database for the period June 2005 to March 2009. Patients with no history in the previous 9 months of myocardial infarction, ischemic stroke, or coronary revascularization were assigned to the ExBID or non-ExBID cohorts. Patients in the non-ExBID cohort received another glucose-lowering drug or combination of drugs, including insulin. Out of a potential pool of more than 1.2 million patients with at least 1 claim for a glucose-lowering drug, 21,754 patients met all eligibility criteria and were included in the ExBID cohort and 361,771 patients were included in the non-ExBID cohort. Exenatide initiators made greater use of other glucose-lowering therapies before the initial exenatide prescription and were also more likely to have obesity, diabetic retinopathy, peripheral neuropathy, hyperlipidemia, hypertension, and ischemic heart disease than nonexenatide initiators.

The analysis showed that patients in the ExBID cohort were significantly less likely to have a CVD event or hospitalizations than those in the non-ExBID cohort.⁴ Hazard ratios for exenatide-treated patients were 0.81 for a CVD event, 0.88 for CVD hospitalization, and 0.94 for all-cause hospitalization. The investigators speculated that this reduction in CVD events and hospitalization may have resulted from greater reduction of hyperglycemia with less hypoglycemia and/or improvement in risk factors, including weight, BP, and lipids. According to clinicaltrials.gov, long-term prospective studies are now evaluating the effects of GLP-1 agonists on cardiovascular outcomes.

The most frequently reported adverse effects of GLP-1 agonist treatment are GI disorders, which are usually dose related, mild to moderate intensity, and transient. In phase 3 clinical trials, reported ranges for the most common GI adverse events during monotherapy and combination therapy, respectively, were: nausea, 8% to 28% and 8% to 44%; diarrhea, 1% to 17% and 6% to 20%; and vomiting, 4% to 11% and 4% to 18%. With ExBID and liraglutide, following the manufacturers’ recommendations about dose titration can reduce the risk of GI disturbance. Since the GLP-1 agonists are administered by subcutaneous injection, patients may experience mild reactions, such as rash and erythema, at the injection site. Patients treated with ExQW may also develop small, asymptomatic injection-site nodules, which are caused by the microspheres used in the product. In phase 3 clinical trials, the incidence of injection-site reactions was approximately 13% with ExBID, 2% with liraglutide, and 17% with ExQW. The risk of developing injection-site reactions can be minimized by following the instructions in the medication guide for each product.

Since it promotes insulin secretion in a glucose-dependent manner, GLP-1 agonist therapy is associated with a low risk of hypoglycemia.\(^1\) According to the 2012 ADA–EASD position statement, this is one of the most valuable features of the GLP-1 agonists.\(^2\) The table shows the incidence of hypoglycemia in core phase 3 clinical trials.\(^3\)–\(^5\) In monotherapy trials, the incidence of minor hypoglycemia ranged from 2% to about 10%. No episodes of major hypoglycemia were reported. Beyond the carefully managed setting of a clinical trial, however, patients receiving GLP-1 agonist monotherapy occasionally experience major hypoglycemia.\(^2\) During the phase 3 clinical trials in which patients received a GLP-1 agonist in combination with at least 1 other glucose-lowering drug, the incidence of minor hypoglycemia ranged from 1.3% to 35.7%, and the incidence of major hypoglycemia ranged from 0.4% to 2.2%.\(^3\)–\(^5\)

During combination therapy, the risk of hypoglycemia is highest when a GLP-1 agonist is used with a sulfonylurea and intermediate when it is used with basal insulin.\(^3\)–\(^5\) Therefore, patients receiving a GLP-1 agonist and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia.\(^3\)–\(^5\) Reducing the dose of any other concomitantly administered insulin secretagogue, such as a meglitinide, would also be prudent. In addition, health care providers should consider reducing the insulin dose when a patient at increased risk of hypoglycemia is taking a GLP-1 agonist in combination with basal insulin.\(^3\)–\(^4\)

### Incidence (%) of Hypoglycemia in Core Phase 3 GLP-1 Agonist Trials

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ExBID 5 µg(^1)</td>
<td>ExBID 10 µg(^1)</td>
</tr>
<tr>
<td></td>
<td>ExBID 5 µg(^1)</td>
<td>ExBID 10 µg(^1)</td>
</tr>
<tr>
<td>Minor</td>
<td>5.2</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>4.5–19.2</td>
<td>5.3–35.7</td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not classified</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Patients receiving a GLP-1 agonist and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia.\(^1\)–\(^3\)
- Health care providers should consider reducing the dose of insulin when a patient at increased risk of hypoglycemia is taking a GLP-1 agonist in combination with basal insulin.\(^1,2\)

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During clinical trials and the postmarketing period, GLP-1 agonist therapy has been associated with infrequent cases of chronic and acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis.\(^1\)\(^-\)\(^3\) A recent meta-analysis found that patients with type 2 diabetes have an 84% greater risk of acute pancreatitis than people without diabetes.\(^4\) Moreover, some patients who have developed pancreatitis in association with GLP-1 agonist therapy had other risk factors, such as a history of cholelithiasis or alcohol abuse.\(^2\) A population-based case-control study that adjusted for these risk factors found that treatment with an incretin-based therapy (ExBID or sitagliptin) was associated with statistically significantly higher odds of acute pancreatitis than other treatments for type 2 diabetes.\(^5\)

When initiating GLP-1 agonist therapy or making dose increases, health care providers should observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting.\(^1\)\(^-\)\(^3\) Patients should be instructed to discontinue GLP-1 agonist treatment and contact their health care provider immediately if they experience possible symptoms of pancreatitis.\(^1\)\(^-\)\(^3\) Should pancreatitis be confirmed, GLP-1 agonist treatment should not be restarted. For patients with a history of pancreatitis, the prescribing information for liraglutide recommends that it be used with caution\(^2\) and the prescribing information for ExBID\(^1\) and ExQW\(^3\) recommends that other glucose-lowering options be considered.

Both liraglutide and ExQW cause thyroid C-cell tumors in rodents.\(^2\)\(^,\)\(^3\) It is not currently known whether these agents cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. As of March 2013, liraglutide and ExQW (but not ExBID) are contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Patients should be counseled regarding the risk and symptoms of thyroid tumors before beginning treatment with liraglutide or ExQW.

As previously mentioned, the FDA recently approved the use of ExBID and liraglutide in combination with basal insulin.\(^1,2\) (As of March 2013, ExQW did not have this indication.\(^3\)) The ExBID approval was based on a double-blind, placebo-controlled, multicenter, 30-week trial in which 137 patients were randomized to receive ExBID at a dose of 10 µg with insulin glargine and 122 patients were randomized to receive placebo with insulin glargine.\(^4\) Compared to insulin glargine and placebo, treatment with insulin glargine and ExBID resulted in a greater reduction in mean A1C from baseline at end point and a higher percentage of patients whose A1C was below 7%.\(^1,4\) The mean weight change from baseline was a decrease of 1.8 kg in the ExBID group and an increase of 1.0 kg in the placebo group.\(^4\) The incidence of minor hypoglycemia was similar—25% with ExBID and 29% with placebo. No patients in the ExBID group and one patient in the placebo group experienced major hypoglycemia. The discontinuation rate due to AEs was significantly higher in the ExBID group (9.5%) than in the placebo group (0.8%).

Approval of the use of liraglutide with basal insulin was based on a sequential intensification trial in which liraglutide was added to metformin and given for 12 weeks, followed by a 26-week, randomized, open-label investigation of further treatment with systematically titrated insulin detemir in patients whose A1C remained 7% or greater.\(^5\) From baseline to end point of the 26-week study period, patients randomized to insulin detemir had a mean A1C reduction of 0.5%, whereas those randomized to the control group had a mean increase of 0.02%. Also at end point, 43% of patients in the insulin detemir group and 17% of those in the control group attained an A1C of less than 7%. Mean weight loss over 26 weeks was 0.2 kg with insulin detemir and 1.0 kg with liraglutide and metformin only. The incidence of minor hypoglycemia was 9.2% in the insulin detemir group compared with 1.3% in the control group. Two percent of the insulin detemir group and four percent of the control group discontinued due to AEs.

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Benefits of GLP-1 Agonist Therapy Are Durable

- Studies in which a GLP-1 agonist was administered for 1 to 3.5 years showed that long-term treatment results in sustained improvement from baseline in mean
  - A1C levels¹–⁶
  - Weight¹–⁶
  - Blood pressure¹–⁶
  - Levels of many serum lipids*¹,⁴–⁶
- Long-term treatment is safe and well tolerated¹–⁶
  - Incidence of nausea gradually diminished in some studies²–⁴,⁶
  - Clinically significant safety or tolerability issues did not emerge over time,¹–⁶ except for injection-site nodules in 6% of patients treated with ExQW⁶

*Lipid effects not reported for studies 2 and 3.


The benefits of GLP-1 agonist therapy are durable. Studies with ExBID,¹ liraglutide²–⁴ or ExQW⁵,⁶ in which a GLP-1 agonist was administered for 1 year to 3.5 years have shown that long-term treatment results in sustained improvement from baseline in mean A1C,¹–⁶ weight,¹–⁵ blood pressure,¹–⁶ and levels of many serum lipids.¹,⁴–⁶ Effects on lipid levels were not reported for all studies.²,³

These clinical trials also showed that long-term treatment with a GLP-1 agonist is safe and generally well tolerated.¹–⁶ The incidence of nausea, which was often the most frequently reported adverse event,¹–⁴ gradually diminished in some studies.²–⁴,⁶ For the most part, clinically significant safety or tolerability issues did not emerge over time.¹–⁶ An exception was injection site nodule, which was reported in 6% of ExQW-treated patients after 84 weeks.⁶
Several phase 3 clinical trials have compared the efficacy and safety of the different GLP-1 agonists. The first was LEAD-6, a 26-week, randomized, open-label, multinational study that enrolled patients who had inadequate glycemic control while receiving maximally tolerated doses of metformin, a sulfonylurea, or both. Patients were randomized to receive liraglutide 1.8 mg or ExBID 10 μg, along with their prestudy glucose-lowering drugs. At end point, liraglutide-treated patients had a significantly greater mean reduction in A1C levels and a nonsignificantly greater reduction in mean weight than patients treated with ExBID. A significantly greater proportion of patients in the liraglutide group had an A1C value of less than 7%. Rates of minor and major hypoglycemia and nausea were similar with liraglutide and ExBID, but nausea resolved more quickly with liraglutide.

The DURATION-5 trial was a 24-week, randomized, open-label study that was conducted in the US. It compared the safety and efficacy of ExQW 2 mg with that of ExBID 10 μg in patients who were also receiving metformin, a sulfonylurea, a TZD, or a combination of these medications. At end point, patients in the ExQW group had a statistically significantly greater reduction in the mean A1C level, and a significantly greater proportion of patients had an A1C of less than 7%. Mean weight reduction was nonsignificantly greater in the ExQW group. The incidence of minor hypoglycemia was similarly low in the 2 treatment groups, and no instances of major hypoglycemia were reported. The incidence of nausea was more than twice as high in the ExBID group.

The third comparative trial was DURATION-6, which compared ExQW 2 mg to liraglutide 1.8 mg. Participants in this 26-week, open-label, multinational study could also receive metformin, a sulfonylurea, pioglitazone, or any combination of these agents. At end point, the mean A1C reduction from baseline was significantly greater with liraglutide and a significantly greater proportion of liraglutide-treated patients attained an A1C of less than 7%. Mean weight loss was nonsignificantly greater with liraglutide. The incidence of minor hypoglycemia was similar in the 2 groups, and no episodes of major hypoglycemia were reported. The incidence of nausea was more than 2-fold higher with liraglutide.

This case describes a patient who is an appropriate candidate for treatment with a GLP-1 agonist.

Robert is a 52-year-old African American male who returns to his healthcare provider for a routine physical examination. He is married and has 2 adult sons, one of whom is married and has an infant daughter. He works as a trainer for a large corporation, a job that requires extensive local and national travel.

Robert is 70 inches tall, weighs 225 pounds, and has a BMI of 32.3 kg/m$^2$, putting him in the obese range. He has gained 10 pounds over the past year. He attributes this weight gain to eating frequently in restaurants and eating vending-machine snack food in the mid-afternoon when he feels low on energy. Between his work schedule, considerable time spent in the car on most days, and frequent air travel, he says that he has no time for physical activity.

Robert was diagnosed with type 2 diabetes 5 years ago. Currently he has no diagnosed diabetes complications. Testing last year revealed normal renal function. He has no other health issues.
Robert’s current glucose-lowering regimen is metformin 1000 mg twice daily and glipizide extended release 10 mg once daily. Both agents are well tolerated. As the table shows, Robert’s blood glucose values, blood pressure (BP), and lipid levels do not meet current ADA goals. His A1C is 8.4%, his fasting plasma glucose (FPG) level is 187 mg/dL, and his postprandial glucose (PPG) value was not measured. Thus, his A1C level exceeds the general ADA target by 1.4% and his FPG exceeds the high end of the generally recommended range by 57 mg/dL.¹

Robert’s BP is 146/93, whereas the ADA currently recommends values of <140/80.¹ Recall that the ADA standards also state that patients with confirmed BP ≥140/80 should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve BP goals. Thus, Robert is a candidate for antihypertensive drug therapy as well as lifestyle modification. The ADA recommends either an ACE inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy for patients with hypertension and diabetes.

Robert’s LDL-C value is 114 mg/dL, and thus exceeds the ADA target for patients without overt cardiovascular disease by 14 mg/dL.¹ His HDL-C value is 33 mg/dL and is thus 7 mg/dL below the recommended value of 40 mg/dL for men. His triglyceride level is 194 mg/dL, thus exceeding the ADA-recommended value of 150 mg/dL by 44 points. Recall that the ADA recommends statin therapy, regardless of baseline A1C levels, for patients with diabetes who do not have overt cardiovascular disease (CVD) but who are over age 40 and have one or more other CVD risk factors, such as hypertension and dyslipidemia. Thus, Robert is also a candidate for statin therapy.

In determining the optimal treatment regimen for Robert, several considerations are especially important. His A1C and FPG are not at goal and it is probable that his PPG level also exceeds the ADA goal of <180 mg/dL. Additionally, he has obesity, mild hypertension, and dyslipidemia.

There are a number of treatment options for Robert. His metformin dose could be increased from 2000 mg/day to the maximum dose of 2500 mg/day, but this small increase would probably not have a substantial effect on his blood glucose (BG) values. Additionally, the maximum clinically effective dose of metformin is 1000 mg twice daily. His dose of glipizide extended release could be increased from 10 mg/day to the maximum dose of 20 mg/day. This dose escalation might have a beneficial effect on his BG values, but it would probably not be sufficient to bring Robert to goal. Furthermore, this approach could lead to further weight gain and episodes of hypoglycemia, which would be very undesirable for someone who spends much of his time driving a car. Adding a TZD to Robert’s regimen might bring his BG values to goal, but it could also result in additional weight gain. Adding a DPP-4 inhibitor would reduce Robert’s BG levels, but probably not sufficiently. Furthermore, DPP-4 inhibitor therapy would probably not reduce his weight.

Considering Robert’s overall situation, adding a GLP-1 agonist is his best option. It might bring his BG values to goal while also exerting beneficial effects on his weight, BP, and lipid levels. Since Robert’s BP is 146/93, he should begin antihypertensive therapy with either an ACE inhibitor or an ARB. Additionally, since he is over age 40 and has hypertension, it would be appropriate for Robert to begin statin therapy even if his lipid values met ADA goals.

Robert’s health care provider also referred him to a registered dietitian for medical nutrition therapy (MNT). Robert was very pleased with this referral, since it would give him the opportunity to learn about safe weight loss options, nutritious food choices that would boost his energy level in the afternoon, and healthy restaurant eating. The health care provider also encouraged him to look for opportunities to get some aerobic exercise as part of his daily routine, such as taking a brisk walk at lunchtime and walking around the airport while waiting for flights.

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**Case 1: Considerations in Selecting a Treatment Regimen**

- Robert’s A1C and FPG are not at goal
- He has obesity, mild hypertension, and dyslipidemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase MET dose from 2000 mg/d to maximum (2500 mg/d)</td>
<td>Unlikely to have substantial effect on BG values</td>
</tr>
<tr>
<td>Increase glipizide extended release dose from 10 mg/d to maximum (20 mg/d)</td>
<td>Might have beneficial effect on BG values, but could also lead to further weight gain and hypoglycemia</td>
</tr>
<tr>
<td>Add a TZD</td>
<td>Might bring BG values to goal, but could result in further weight gain</td>
</tr>
<tr>
<td>Add a DPP-4 inhibitor</td>
<td>Might reduce BG levels, but probably not sufficiently; unlikely to affect weight</td>
</tr>
<tr>
<td>Add a GLP-1 agonist</td>
<td>Might bring BG values to goal and have beneficial effects on weight, BP, and lipids</td>
</tr>
<tr>
<td>Add an ACE inhibitor or an ARB</td>
<td>Combined with MNT, likely to bring BP to goal</td>
</tr>
<tr>
<td>Add a statin</td>
<td>Combined with MNT, likely to bring lipid levels to goal</td>
</tr>
</tbody>
</table>

After learning about GLP-1 agonist therapy and how to use a disposable pen, Robert began receiving a glucose-lowering regimen that included 3 agents. Following titration of the GLP-1 agonist, his new regimen included metformin 1000 mg twice daily, glipizide extended release 5 mg once daily, and liraglutide 1.2 mg once daily. Note that Robert’s former dose of glipizide was reduced by 50%, an approach recommended when a sulfonylurea is administered together with an incretin-based therapy to reduce the risk of hypoglycemia. Robert also began antihypertensive therapy, taking captopril at a dose of 25 mg twice daily, and statin therapy, taking simvastatin at a dose of 20 mg once daily.

Robert found MNT to be very helpful, and lost 9 pounds over a 3-month period. He said that he had become very creative about finding ways to get extra exercise, such as taking the stairs rather than the elevator at work and leaving his car at the far end of parking lots.

Robert had substantial improvement in his BG, BP, and lipid levels after 3 months of treatment with his new medication regimen. In the table, values that are at goal are shown in green and those that are not at goal are shown in red. Although Robert’s A1C still exceeded the A1C goal, it had decreased by 1.1% and was 7.3%—nearly at goal. At 139 mg/dL, his FPG was approaching the recommended range and his PPG was at goal. Weight loss and treatment with an ACE inhibitor and a GLP-1 agonist appear to have had beneficial effects on Robert’s BP. At 135/79, both his SBP and his DBP were within the recommended range. Weight loss and treatment with a statin and a GLP-1 agonist also seem to have had a favorable effect on Robert’s lipid levels. His LDL-C level fell from 114 to 95 mg/dL and thus was at goal. His HDL-C level rose to 37 mg/dL and thus approached the ADA target of 40 mg/dL for men. His triglyceride level decreased by 31 mg/dL, to 163 mg/dL. Although this value remained above target, it was greatly improved.

In view of the substantial progress he has made and the fact that all values are at or approaching goal, Robert will continue his current regimen for 3 more months. At that point a decision will be made about whether his regimen of glucose-lowering agents should be modified in some way and whether his doses of captopril and simvastatin should be changed.
Typical effects of GLP-1 agonist therapy include __________.

a. weight loss and a slight reduction in the heart rate
b. a minimal risk of hypoglycemia when given with a sulfonylurea and a modest reduction in DBP
c. possible nausea that often diminishes over time and reduced triglyceride levels
d. a modest increase in SBP and a low risk of hypoglycemia when given as monotherapy
The correct answer is c.

Typical effects of GLP-1 agonist therapy include possible nausea that often diminishes over time and reduced triglyceride levels.
DPP-4 INHIBITORS
This table shows the four DPP-4 inhibitors that were approved for use in the US as of March 2013. Sitagliptin, the first DPP-4 inhibitor to be introduced in the US, has the brand name Januvia. It is manufactured by Merck & Co., Inc. and was approved by the FDA on October 16, 2006. Saxagliptin, marketed under the name Onglyza, is manufactured by Bristol-Myers Squibb Company. It received FDA approval on July 31, 2009. Linagliptin has the brand name Tradjenta and is marketed by Boehringer Ingelheim Pharmaceuticals, Inc. It was approved by the FDA on May 2, 2011. Alogliptin, which is marketed under the name Nesina, is manufactured by Takeda Pharmaceutical Company Limited. It received FDA approval on January 25, 2013.

Each of these DPP-4 inhibitors is indicated as an adjunct to meal planning and exercise to improve glycemic control in adults with type 2 diabetes.

Vildagliptin, another DPP-4 inhibitor, has been approved for use in many countries, but not the US. Vildagliptin is discussed briefly on the next slide. Other DPP-4 inhibitors are now under development. Investigational DPP-4 inhibitors will not be discussed in this activity.

Vildagliptin

- Approved in more than 70 countries, but not in US\(^1\)
- Standard doses\(^2\)
  - 50 mg BID: monotherapy or with metformin or a TZD
  - 50 mg QD (in the morning): with a sulfonylurea
- Doses for special populations\(^2\)
  - 50 mg QD in patients with moderate or severe renal impairment or ESRD
  - Should not be used in patients with hepatic impairment, including patients with pretreatment ALT or AST values greater than 3 × ULN
- Also available as a fixed-dose combination product with metformin\(^3\)

<table>
<thead>
<tr>
<th>ALT</th>
<th>AST</th>
<th>BID</th>
<th>QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>alanine aminotransferase</td>
<td>aspartate aminotransferase</td>
<td>twice daily</td>
<td>once daily</td>
</tr>
</tbody>
</table>

\(^3\) Eucreas. Summary of product characteristics. 2012.

Vildagliptin, another DPP-4 inhibitor, is approved in more than 70 countries, including the member states of the European Union (EU).\(^1\) Its proprietary name in most countries is Galvus.\(^2\) US approval of vildagliptin was delayed pending submission of additional data on its effect on liver enzyme levels, and Novartis, its manufacturer, is no longer pursuing FDA approval.\(^2,3\) Nevertheless, US health care providers should have some knowledge of vildagliptin, since visitors to this country may be taking it.

In the EU, vildagliptin is indicated as monotherapy in patients for whom metformin is inappropriate due to contraindications or intolerance.\(^2\) It is also indicated as dual therapy in combination with metformin, a sulfonylurea, or a TZD.\(^2\) Recommended standard doses and doses for special populations are shown on the slide.

Vildagliptin is also available as a fixed-dose combination product with metformin; its most common proprietary name is Eucreas.\(^4\) Two dose strengths are available in the EU: vildagliptin 50 mg with metformin hydrochloride 850 mg and vildagliptin 50 mg with metformin hydrochloride 1000 mg.\(^4\)

We will not discuss vildagliptin further in this activity, but several recent, comprehensive review articles are included in the reference list that accompanies the PowerPoint presentation.

This table highlights important pharmacologic and pharmacokinetic characteristics of the DPP-4 inhibitors. Ex vivo studies using human plasma showed that all of these agents are potent inhibitors of DPP-4, with maximum inhibition ranging from 80% to 97% and inhibition remaining in the 70% to 80% range at 24 hours postdose.\(^1\) None of the DPP-4 inhibitors have shown significant inhibitory activity on other important enzymes, such as DPP-8 or DPP-9.\(^1\)

Although sitagliptin, linagliptin, and alogliptin are not appreciably metabolized,\(^2,3\) saxagliptin is hepatically transformed by cytochrome P450 (CYP) isoenzymes 3A4 and 3A5 to produce the active metabolite 5-hydroxy saxagliptin.\(^1,4\) Ketoconazole significantly increases saxagliptin exposure, and clinically relevant increases in saxagliptin plasma concentrations are anticipated with other strong CYP3A4/5 inhibitors, such as clarithromycin, itraconazole, and ritonavir.\(^4\) The usual recommended daily dose of saxagliptin is 2.5 mg or 5 mg, but the dose should be limited to 2.5 mg during coadministration with a strong CYP3A4/5 inhibitor.\(^4\) Although linagliptin is not appreciably metabolized, it is a CYP3A4 and P-glycoprotein (P-gp) substrate, and coadministration with a strong inducer of CYP3A4 or P-gp such as rifampin may reduce its efficacy.\(^3\) Therefore, patients who must take a CYP3A4 or P-gp inducer should use a different glucose-lowering agent.\(^3\)

Another important difference among the DPP-4 inhibitors involves their elimination pathways. Unlike sitagliptin, saxagliptin, and alogliptin, which are primarily eliminated by the kidney,\(^2,4\) linagliptin is eliminated almost entirely by the liver.\(^3\) Therefore, in contrast to the other DPP-4 inhibitors,\(^2,4,5\) linagliptin can be given without dose modification to patients with any degree of renal impairment.\(^3\) Dose modifications with the DPP-4 inhibitors are discussed further on the next slide.

All DPP-4 inhibitors are formulated as tablets and should be taken orally, once daily, with or without food.\(^1\text{–}^4\) According to current prescribing information, sitagliptin tablets must not be split, crushed, or chewed before swallowing,\(^1\) and saxagliptin tablets must not be split or cut.\(^2\) Dose titration at the beginning of therapy is not required.\(^1\text{–}^4\)

The standard dose of sitagliptin is 100 mg.\(^1\) The dose should be reduced to 50 mg for patients with moderate renal impairment (CrCl ≥30 to <50 mL/min) and to 25 mg for those with severe renal impairment (CrCl <30 mL/min) or ESRD. Candidates for sitagliptin, saxagliptin, or alogliptin therapy should have their renal function assessed before beginning treatment and periodically thereafter to ensure that dose modification is not needed.\(^1\text{,}^2\text{,}^4\) No sitagliptin dose adjustment is needed for patients with mild or moderate hepatic insufficiency.\(^1\) There is no reported clinical experience with sitagliptin or alogliptin in patients with severe hepatic insufficiency.\(^1\text{,}^4\) Saxagliptin should be administered at a dose of 2.5 mg or 5 mg.\(^2\) Patients with moderate or severe renal impairment and those with ESRD should receive the 2.5 mg dose. As mentioned previously, the 2.5 mg dose is also recommended when saxagliptin is taken in combination with a strong CYP3A4/5 inhibitor. No dosage adjustment is recommended for patients with any degree of hepatic impairment. The recommended dose of linagliptin is 5 mg.\(^3\) No dose adjustment is recommended for patients with any degree of renal or hepatic impairment. As previously mentioned, linagliptin should not be used by patients who require treatment with a strong CYP3A4 or P-gp inducer. The standard dose of alogliptin is 25 mg.\(^4\) The daily dose should be reduced to 12.5 mg for patients with moderate renal impairment (defined for this drug as CrCl ≥30 to <60 mL/min) and to 6.25 mg for those with severe renal impairment (CrCl ≥15 to <30 mL/min) or ESRD. Alogliptin should be used with caution in patients with liver disease.

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### Approved Doses of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard Dose, mg</th>
<th>Moderate Renal Impairment, mg</th>
<th>Severe Renal Impairment or ESRD, mg</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin(^1)</td>
<td>100</td>
<td>50</td>
<td>25</td>
<td>No experience in patients with severe hepatic insufficiency</td>
</tr>
<tr>
<td>Saxagliptin(^2)</td>
<td>2.5 or 5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5 mg with strong CYP3A4/5 inhibitor</td>
</tr>
<tr>
<td>Linagliptin(^3)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>Do not take with strong CYP3A4 or P-gp inducer</td>
</tr>
<tr>
<td>Alogliptin(^4)</td>
<td>25</td>
<td>12.5</td>
<td>6.25</td>
<td>No experience in patients with severe hepatic insufficiency, use with caution in patients with liver disease</td>
</tr>
</tbody>
</table>

*Assess renal function before initiating therapy and periodically thereafter.

This slide shows mean A1C reductions from baseline at the end points of phase 3 clinical trials of DPP-4 inhibitors. The duration of most studies was 24 to 26 weeks, but studies extended from 18 to 54 weeks.\textsuperscript{1–4} Mean A1C reductions ranged from 0.4% to 1.0% in monotherapy trials and from 0.3% to 2.4% in combination trials. Overall, the greatest reductions occurred when a DPP-4 inhibitor was administered with a TZD, with or without metformin and/or a sulfonylurea. The largest reduction, of 2.4%, occurred in a randomized, double-blind, 24-week study that assessed the efficacy of sitagliptin as initial therapy in combination with pioglitazone.\textsuperscript{1} (Note that initial therapy trials enroll patients who have no, or minimal, prior exposure to glucose-lowering drugs.) Overall, administering a DPP-4 inhibitor in combination with a sulfonylurea resulted in the lowest mean A1C reduction.

Collectively, the results of these studies show that the mean A1C reductions attained with the DPP-4 inhibitors are somewhat smaller than those observed with the GLP-1 agonists.

In clinical trials, the DPP-4 inhibitors have demonstrated a generally neutral effect on weight.\(^1,2\) Small beneficial effects on blood pressure and serum lipid levels have been shown in some, but not all studies.\(^1,2\)

The results of large meta-analyses suggest that treatment with a DPP-4 inhibitor may reduce the risk of cardiovascular events, such as myocardial infarction.\(^3,4\) Large outcome trials to establish the cardiovascular effects of the DPP-4 inhibitors are now underway\(^1\) These include the TECOS trial with sitagliptin, the SAVOR-TIMI 53 study with saxagliptin, the CAROLINA trial with linagliptin, and the EXAMINE study with alogliptin.\(^1\)

According to the 2012 ADA–EASD position statement, one of the main advantages of the DPP-4 inhibitors is that they are well tolerated. During phase 3 placebo-controlled clinical trials, the overall incidence of adverse reactions with a DPP-4 inhibitor was similar to that of placebo.

The table shows the frequency of adverse reactions reported in at least 5% of patients and more commonly than in patients given placebo in core phase 3 studies. Note that a range of values is given for sitagliptin because data from individual studies are reported in the prescribing information. In contrast, a single value is given for saxagliptin and linagliptin because pooled safety data are reported in their prescribing information. No data are shown for alogliptin because pooling of safety data did not identify any adverse reactions that were reported in at least 5% of alogliptin-treated patients and more frequently than in patients given placebo. However, the adverse reactions reported with the highest frequency and in more patients receiving alogliptin than placebo were similar to those reported with the other DPP-4 inhibitors—nasopharyngitis (4.4%), headache (4.2%), and upper respiratory tract infection (URT1) (4.2%). Note that all of the adverse reactions shown in the table are conditions that are prevalent in the general population: headache, nasopharyngitis, URT1, and urinary tract infection. No important differences in the overall safety profiles of the various DPP-4 inhibitors have so far emerged.

This table shows the reported incidence of hypoglycemia in phase 3 clinical trials of the DPP-4 inhibitors. In monotherapy trials, the incidence of minor hypoglycemia ranged from 0.3% to 5.6%, and no major episodes were reported. In trials in which a DPP-4 inhibitor was given in combination with one or more agents, the incidence of minor hypoglycemia ranged from 0% to 26.9%, and the incidence of major hypoglycemia ranged from 0% to 2.7%.

No major differences emerged among the DPP-4 inhibitors with respect to hypoglycemia. Because higher rates of hypoglycemia were reported when a DPP-4 inhibitor was administered with a sulfonylurea or insulin, the product information for each agent advises that during coadministration of a DPP-4 inhibitor with an insulin secretagogue or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

Note: Full citations for the following references are given in the Reference List for this activity.

Infrequent cases of acute pancreatitis and hypersensitivity reactions (HSRs) have been reported in patients treated with a DPP-4 inhibitor during clinical trials and the postmarketing period. A meta-analysis of core clinical trials did not detect a higher incidence of pancreatitis in patients who received a DPP-4 inhibitor than in those who received a comparator. However, as previously mentioned, a case-control study found that treatment with an incretin-based therapy (sitagliptin or ExBID) was associated with statistically significantly higher odds of acute pancreatitis than other treatments for type 2 diabetes. As during GLP-1 agonist therapy, health care providers should monitor their patients for signs and symptoms of pancreatitis, especially at the start of treatment. If pancreatitis is suspected, the DPP-4 inhibitor should be discontinued promptly and appropriate management initiated. Patients should be instructed to discontinue treatment and contact their health care provider immediately if they experience possible symptoms of pancreatitis.

Serious hypersensitivity reactions reported in patients treated with a DPP-4 inhibitor include anaphylaxis, angioedema, and severe cutaneous adverse reactions, including Stevens-Johnson syndrome. These reactions often occur within the first 3 months of treatment, and can occur after the first dose. Some evidence suggests that the risk of an HSR increases during concomitant treatment with an ACE inhibitor and perhaps with an ARB. If a serious HSR is suspected during DPP-4 inhibitor therapy, that DPP-4 inhibitor must be permanently discontinued, since resumption of treatment is contraindicated. Health care providers should use caution when prescribing a DPP-4 inhibitor for a patient who has already experienced a HSR during treatment with another member of this class.

The DPP-4 inhibitors have been approved as add-on combination therapy with basal insulin.¹–⁴ The basis for each approval was a 24- or 26-week, randomized, double-blind, placebo-controlled trial in which sitagliptin 100 mg, saxagliptin 5 mg, linagliptin 5 mg, or alogliptin 25 mg was added to the regimen of patients who were already taking some type of basal insulin. Patients in all 4 studies could also take metformin.¹–⁴ In addition, patients in the linagliptin study could take pioglitazone, with or without metformin.³ The goal in each trial was to maintain a stable dose of insulin throughout the study period, but investigators could change the dose if prespecified glycemic targets were not met.¹–⁴

The table shows that add-on therapy with a DPP-4 inhibitor resulted in a further A1C reduction of 0.6% to 0.7%.¹–⁴ At least twice as many patients in the DPP-4 inhibitor group compared to the placebo group attained an A1C of less than 7%, although the percentage of patients who reached this goal was consistently small. In all groups except the placebo group of the saxagliptin study, the mean insulin dose remained relatively stable between baseline and end point.²,³,⁵,⁶ In all but the sitagliptin study, the incidence of minor hypoglycemia was similar in the DPP-4 inhibitor and placebo groups.¹,⁷–⁹ In the sitagliptin study, the incidence of minor hypoglycemia was higher in the sitagliptin group than in the placebo group, although the overall incidence of minor hypoglycemia was low.¹ The incidence of major hypoglycemia was uniformly low, confirming the safety of combination therapy with a DPP-4 inhibitor and basal insulin.¹,⁷–⁹

Note: Full citations for the following references are given in the Reference List for this activity.

As part of their approval processes, sitagliptin, saxagliptin, and linagliptin were evaluated in randomized, long-term noninferiority trials in which they were compared to a sulfonylurea.\(^1\)–\(^6\)

Sitagliptin and saxagliptin were each compared to glipizide in 52-week trials.\(^1,3\) Linagliptin was compared to glimepiride in a 104-week trial that included an interim data analysis at 52 weeks.\(^5\)

Participants in each trial had suboptimal glycemic control on metformin at baseline and continued background metformin therapy throughout the study.\(^1,3,5\)

As the table shows, 52-week data were similar for the 3 DPP-4 inhibitors. In each trial, the glucose-lowering efficacy of the DPP-4 inhibitor was noninferior to that of the sulfonylurea.\(^1,3,5\)

Longitudinal data from the sitagliptin and saxagliptin trials suggested that the efficacy of DPP-4 inhibitor-based therapy might be more durable than that of sulfonylurea-based therapy, beginning at about week 24,\(^2,4\) but this difference was not observed in the linagliptin study.\(^6\)

A major finding of each study was that the overall incidence of hypoglycemia was at least 6 times higher in patients treated with a sulfonylurea than in those treated with a DPP-4 inhibitor.\(^2,4,5\)

The findings of these studies provide evidence for the efficacy of long-term DPP-4 inhibitor therapy in combination with metformin without undue hypoglycemia.

The long-term efficacy and safety of alogliptin were assessed in a 52-week, randomized, active-comparator study that enrolled patients whose diabetes was inadequately controlled on a regimen of pioglitazone 30 mg and metformin at a dose of at least 1500 mg per day or at the maximum tolerated dose. Following a 4-week single-blind, placebo run-in period, patients were randomized to receive either the addition of alogliptin 25 mg to the current regimen or the titration of pioglitazone 30 mg to 45 mg. Patients who did not meet prespecified glycemic goals during the treatment period received glycemic rescue therapy. The table shows that the efficacy of alogliptin in combination with pioglitazone and metformin was statistically significantly greater than that of uptitrated pioglitazone with metformin, and the percentage of patients with an A1C of less than 7% at end point was significantly higher in the alogliptin group. Eleven percent of patients in the alogliptin group compared with 22% of those in the pioglitazone uptitration group required glycemic rescue. Rates of hypoglycemia were low in both groups, although the incidence of both minor and major hypoglycemia were higher in alogliptin-treated patients. The investigators concluded that this study highlights the value of triple oral therapy with glucose-lowering drugs with distinct, but complementary mechanisms of action.

The FDA has approved a number of fixed-dose combination products that include a DPP-4 inhibitor,1–7 and others are currently under investigation. The table shows products approved by the FDA as of March 2013. Note that all of the approved DPP-4 inhibitors are available with metformin, and that the availability of immediate- and extended-release products varies.

Sitagliptin in combination with simvastatin, which is marketed in the US as Juvisync™, is the first FDA-approved product to combine a DPP-4 inhibitor with a statin.3 This product is indicated for patients with type 2 diabetes who require statin therapy for the treatment of dyslipidemia and/or for cardiovascular risk reduction.3 Patients with severe renal impairment who require the 25 mg dose of sitagliptin should not use this combination product because that dosage strength is currently unavailable.3

Alogliptin plus pioglitazone, which is marketed as Oseni™, is the first FDA-approved product to combine a DPP-4 inhibitor with pioglitazone.7 When prescribing this product, refer to the detailed recommendations for starting doses included in the Dosage and Administration section of the prescribing information.7

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**Approved Fixed-Dose Combination Products with a DPP-4 Inhibitor**

<table>
<thead>
<tr>
<th>Product (Brand Name)</th>
<th>Available Dose Forms and Strengths</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin + metformin (Janumet®)</td>
<td>SITA/MET 50/500, 50/1000 mg</td>
<td>3/30/07²</td>
</tr>
<tr>
<td>Sitagliptin + metformin ER (Janumet® XR)</td>
<td>SITA/MET 50/500, 50/1000, 100/1000 mg</td>
<td>2/2/12²</td>
</tr>
<tr>
<td>Sitagliptin + simvastatin (Juvisync™)</td>
<td>SITA/SIMVA 50/10, 50/20, 50, 100/10, 100/20, 100/40 mg</td>
<td>10/7/11²</td>
</tr>
<tr>
<td>Saxagliptin + metformin ER (Kombiglyze™ XR)</td>
<td>SAXA/MET 2.5/1000, 5/500, 5/1000 mg</td>
<td>11/5/10²</td>
</tr>
<tr>
<td>Linagliptin + metformin (Jentadueto™)</td>
<td>LINA/MET 2.5/500, 2.5/850, 2.5/1000 mg</td>
<td>1/30/12²</td>
</tr>
<tr>
<td>Alogliptin + metformin (Kazano™)</td>
<td>ALO/MET 12.5/500, 12.5/1000 mg</td>
<td>1/25/13</td>
</tr>
<tr>
<td>Alogliptin + pioglitazone (Oseni™)</td>
<td>ALO/PIO 12.5/15, 12.5/30, 12.5/45, 25/15, 25/30, 25/45 mg</td>
<td>1/25/13</td>
</tr>
</tbody>
</table>


The first head-to-head comparison of two DPP-4 inhibitors was a double-blind, phase 3b, 18-week multicenter clinical trial in which adults whose BG levels were inadequately controlled with metformin were randomized to receive add-on therapy with saxagliptin 5 mg or sitagliptin 100 mg. 

A total of 403 patients were randomized to the saxagliptin group and 398 patients were randomized to the sitagliptin group. The primary efficacy measure was a comparison of the mean change in A1C from baseline at week 18. The noninferiority of saxagliptin to sitagliptin was confirmed if the upper limit of the 2-sided 95% confidence interval (CI) of the A1C difference between treatments was less than 0.3%. As shown in the graph, mean A1C reductions from baseline at week 18 were 0.52% with saxagliptin and 0.62% with sitagliptin. The between-group difference was 0.09% and the 95% CI was -0.01 to 0.20%. Therefore, saxagliptin met the criterion for noninferiority to sitagliptin.

The table shows that the incidence of AEs was similar in the saxagliptin and sitagliptin groups and that the pattern of AEs was similar to that seen in other studies of DPP-4 inhibitors. Collectively, the most commonly reported AEs were minor infections involving the respiratory system and urinary tract. The incidence of minor hypoglycemia was about 3% in each group. The incidence of major hypoglycemia was 0% with saxagliptin and 0.3% with sitagliptin.

This case describes a patient who is an appropriate candidate for treatment with a DPP-4 inhibitor.

Amy is a 63-year-old white female who comes to the clinic for a routine physical examination. She is married and has 2 adult children. She works full-time as a computer specialist at a local university.

Amy is 65 inches tall, weighs 183 pounds, and has a BMI of 30.4 kg/m². Her weight has been stable over the past year. She says that while she usually prepares balanced dinners that are consistent with her food plan, she often makes unwise food choices when she goes out for lunch during the work week. She also says that by the time she gets home from work and makes dinner, she lacks the energy and motivation to exercise. She adds that her weekends are filled with household chores and family visits.

Amy was diagnosed with type 2 diabetes 2 years ago. Currently she has no known diabetes complications. Testing last year revealed normal renal function. Aside from mild seasonal allergic rhinitis, she has no other health issues.

Amy says that she would like to avoid using an injectable glucose-lowering drug, if possible.
Amy’s current glucose-lowering regimen is metformin 500 mg twice daily and glimepiride 8 mg once daily. She tolerates both agents well at their current doses, but has experienced unacceptable nausea with higher doses of metformin.

As the table shows, Amy’s blood glucose values and HDL-C level do not meet ADA targets and her blood pressure, at 133/78 mmHg, is approaching the recommended ceiling of <140/80 mmHg. Her A1C is 7.8%, her FPG is 162 mg/dL, and her PPG is 231 mg/dL. Thus, her A1C level exceeds the general ADA target by 0.8%, her FPG exceeds the high end of the generally recommended range by 32 mg/dL, and her PPG exceeds the general ADA target by 51 mg/dL.\(^1\)

Amy’s LDL-C and triglyceride levels are at goal, although her LDL-C value of 96 mg/dL is approaching the ADA limit of <100 mg/dL for patients without overt cardiovascular disease.\(^1\) At 43 mg/dL, her HDL-C level is below the recommended level of ≥50 mg/dL for women. According to ADA guidelines, Amy should begin statin therapy at this point, since she is more than 40 years of age and has a low HDL level.

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Case 2: Considerations in Selecting a Treatment Regimen

- Amy’s A1C, FPG, and PPG are not at goal
- She has obesity, low HDL-C, and borderline hypertension
- She is already receiving maximum recommended glimepiride dose (8 mg once daily)
- She is eager to avoid an injectable agent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add a TZD</td>
<td>Might bring BG values to goal, but could result in further weight gain</td>
</tr>
<tr>
<td>Add a GLP-1 agonist</td>
<td>Would probably reduce BG levels sufficiently and have beneficial effects on weight, BP, and lipids, but would need to be administered by injection</td>
</tr>
<tr>
<td>Add basal insulin</td>
<td>Would reduce BG levels sufficiently, but could result in additional weight gain and would need to be injected</td>
</tr>
<tr>
<td>Add a DPP-4 inhibitor</td>
<td>Oral medication that would probably bring BG values to goal and would not increase weight</td>
</tr>
<tr>
<td>Add a statin¹</td>
<td>Combined with lifestyle modification, would bring HDL-C to goal</td>
</tr>
</tbody>
</table>


In determining the optimal treatment regimen for Amy, several considerations are important. Her A1C, FPG, and PPG are not at goal. Additionally, she has obesity, low HDL-C, and borderline hypertension. She is already receiving her maximum tolerated daily dose of metformin (1000 mg/d) and the maximum recommended daily glimepiride dose of 8 mg. Amy tolerates glimepiride well, so it seems advisable to keep it as part of her regimen, at least for the immediate future.

At this point there are several treatment options for Amy. Adding a TZD to Amy’s regimen might bring her BG values to goal, but could also result in additional weight gain. Adding a GLP-1 agonist would probably reduce Amy’s blood glucose levels sufficiently and would have beneficial effects on weight, blood pressure, and lipids, but a GLP-1 agonist would need to be administered by injection. While adding basal insulin would have the desired effect on Amy’s BG levels, it could lead to weight gain and would also need to be injected. In the short term, it would be better to try to bring Amy to goal using oral medication.

Considering her overall situation, adding a DPP-4 inhibitor appears to be the best option for Amy. It would probably bring her BG values to goal and would not increase her weight. As already mentioned, Amy should also begin statin therapy since she is over 40 years of age and has a low HDL-C level.¹ When used in conjunction with MNT, statin therapy should bring her HDL-C level to goal.

To help her make more appropriate food choices, especially when she eats away from home, the health care provider refers Amy to a registered dietitian for MNT. The health care provider also discusses the ADA recommendation that people with diabetes perform at least 150 minutes per week of moderate-intensity physical activity. Amy says that the most realistic way for her to accomplish this is to start taking her lunch to work and then to walk briskly for 30 minutes around the campus of the university where she works.

Amy’s new glucose-lowering regimen includes metformin 500 mg twice daily, glimepiride 4 mg once daily, and sitagliptin 100 mg once daily. Note that Amy’s former dose of glimepiride was reduced by 50%, a recommended approach for reducing the risk of hypoglycemia when a sulfonylurea is administered with a DPP-4 inhibitor or a GLP-1 agonist. Amy also began statin therapy, taking pravastatin at a dose of 40 mg once daily.

Thanks to what she learned about food choices in her MNT program and her lunch-hour walks, Amy lost 8 pounds over 3 months, lowering her BMI to 29.1 kg/m². She also experienced marked improvements in her BG values, blood pressure, and lipid levels. Over the 3–month period, Amy’s A1C decreased by 0.9%, falling from 7.8% to 6.9%. Her FPG decreased by 35 mg/dL, dropping from 162 to 127 mg/dL. Thus, both her A1C and FPG are now at the ADA goal.¹ Her PPG decreased by 45 mg/dL, falling from 231 to 186 mg/dL. Therefore, it remains only slightly above goal. With lifestyle modifications and weight loss, Amy’s BP decreased from 133/78. All of her lipid values improved as a result of lifestyle modification and statin therapy, and her HDL-C level, at 49 mg/dL, is almost at goal.

Given the excellent progress she has made and the fact that all values are at or approaching goal, Amy will continue her current regimen for 3 more months. Eventual modifications to her glucose-lowering regimen might include replacing the sulfonylurea with a TZD, substituting a GLP-1 agonist for the DPP-4 inhibitor, or substituting basal insulin for the sulfonylurea.

A factor when considering a DPP-4 inhibitor for a patient with diabetes is that __________.

a. the dose must be titrated upward over a 1–month period
b. A1C reductions are generally greater than those seen with a GLP-1 agonist
c. patients are likely to lose a moderate amount of weight during treatment
d. overall, the DPP-4 inhibitors are very well tolerated
The correct answer is d.

A factor when considering a DPP-4 inhibitor for a patient with diabetes is that overall, the DPP-4 inhibitors are very well tolerated.
COMPARATIVE DATA AND SUMMARY
Several clinical trials comparing the efficacy and safety of a GLP-1 agonist and a DPP-4 inhibitor have been performed, and others are in progress. Pratley and colleagues conducted a 52-week open-label study, consisting of an initial 26-week study period and a 26-week extension. Patients were randomized to receive liraglutide at a dose of 1.2 or 1.8 mg/day or sitagliptin 100 mg/day, all in combination with metformin. Mean baseline A1C values ranged from 8.4% to 8.5%.

At study end point, patients in both liraglutide groups had significantly greater A1C reductions from baseline than patients in the sitagliptin group, and significantly higher proportions of patients in the 2 liraglutide groups had an A1C of <7%.

Weight reduction from baseline was also significantly greater for both liraglutide doses compared to sitagliptin. The incidence of nausea was 22% with liraglutide 1.2 mg/day, 28% with liraglutide 1.8 mg/day, and 6% with sitagliptin. Consistent with the pattern seen in other studies, the frequency of nausea in liraglutide-treated patients declined after the first 3 weeks of treatment and remained low for the rest of the study. Rates of minor hypoglycemia were very low in all groups, ranging from 0.14 to 0.15 episodes per patient per year. Only one patient, in the liraglutide 1.2 mg/day group, experienced an episode of major hypoglycemia.

ExQW 2 mg was compared with sitagliptin 100 mg in 2 randomized, double-blind, double-dummy 26-week clinical trials in the DURATION series.\(^1\:\^2\) In DURATION-2, patients received ExQW, sitagliptin, or pioglitazone as add-on therapy to metformin.\(^1\) Data for the pioglitazone arm are not shown here. In DURATION-4, patients who were naive to glucose-lowering drugs were randomized to receive monotherapy with ExQW, sitagliptin, metformin, or pioglitazone.\(^2\) Data for the metformin and pioglitazone arms are not reported here.

The table shows that the major findings of these clinical trials were similar. In both studies, treatment with ExQW resulted in a statistically significantly greater reduction from baseline in A1C than treatment with sitagliptin.\(^1\:\^2\) Significant differences favoring ExQW were also observed for the percentage of patients who attained an A1C of less than 7% at end point and for the mean weight reduction from baseline. In both studies, the incidence of nausea was more than 2-fold higher in the ExQW group. The incidence of minor hypoglycemia was low in both trials, and no episodes of major hypoglycemia were reported in either trial.

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Incretin-based therapies partially compensate for the impaired incretin effect in type 2 diabetes
- GLP-1 agonists replicate the activities of native GLP-1 but are less susceptible to degradation by DPP-4
- DPP-4 inhibitors limit degradation of endogenous GLP-1, prolonging GLP-1 activity

GLP-1 agonists are administered by subcutaneous injection, are highly effective, promote weight loss, and may cause nausea

DPP-4 inhibitors are administered orally, are moderately effective, have little effect on weight, and are generally well tolerated

Both classes of incretin-based therapy are associated with low rates of hypoglycemia when given as monotherapy and with many combinations of glucose-lowering drugs

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