Continuing Education Discussion Guide

A Guide to Emerging Treatments for Type 2 Diabetes

Focus on Incretin Therapies

Planned and conducted by ASHP Advantage.

Supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc., which was made possible, in part, through collaboration with Eli Lilly, and an independent medical education grant from Bristol-Myers Squibb and AstraZeneca LP.

ASHP ADVANTAGE

Boehringer Ingelheim

Lilly

ADVANCING DIABETES CARE™

Bristol-Myers Squibb

AstraZeneca

A Guide to Emerging Treatments for Type 2 Diabetes: Focus on Incretin Therapies

This continuing education discussion guide is part of an educational initiative designed to provide pharmacists, nurses, nurse practitioners, and diabetic educators with timely education and resources to optimize the team-based management of diabetes.

For additional resources on this topic, including on-demand continuing education offerings, visit www.leadingdiabetescare.org.

The estimated time to complete this activity is 60 minutes. This activity is provided free of charge and is available from January 23, 2014 to April 1, 2015.

Target Audience

This continuing education activity was planned to meet the needs of pharmacists, nurses, nurse practitioners, and diabetes educators.

Learning Objectives

After participating in this knowledged-based educational activity, participants should be able to

1. Describe the rationale for developing incretin agents, including the shortcomings of older antidiabetic drug therapies.
2. Compare and contrast the pharmacology, pharmacokinetics, pharmacodynamics, and safety of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, and review the patient populations for which each type of agent is potentially beneficial.
3. Explain the role of incretin agents in the treatment of type 2 diabetes mellitus based on evidence-based treatment guidelines from authoritative groups.
4. Recommend glycemic goals and drug therapy for an adult with type 2 diabetes mellitus based on his or her characteristics, needs, preferences, and tolerability.

System Requirements

Web Browser: Microsoft Internet Explorer, Mozilla Firefox, Apple Safari or Google Chrome.

Note: Please disable any "pop-up blocker" features.

Software: Adobe Acrobat Reader version 7 or above to view PDF files (If you do not have Acrobat Reader, you can download it for free from http://get.adobe.com reader).

Connection Speed: Cable, DSL, or better of at least 300 kbps.

Reviewers and Disclosures

The assistance of the following reviewers of this educational activity is gratefully acknowledged. In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support and the Accreditation Council for Pharmacy Education's Guidelines for Standards for Commercial Support, ASHP requires that all individuals involved in the development of activity content disclose their relevant financial relationships and that conflicts of interest be identified and resolved prior to delivery of the activity.

The reviewers and planners report the following relationships:

Curtis L. Triplitt, Pharm.D., CDE
Associate Director, Diabetes Research Center, Texas Diabetes Institute; Associate Professor, Department of Medicine, Division of Diabetes; University of Texas Health Science Center at San Antonio, San Antonio, Texas

Dr. Triplitt declares that he serves on the speakers bureau for Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals and Eli Lilly, and Gilead.

Susan R. Dombrowski, M.S., B.S.Pharm., *Writer*
Ms. Dombrowski declares that she has no relationships pertinent to this activity.

Kristi N. Hofer, Pharm.D., *Staff*
Dr. Hofer declares that she has no relationships pertinent to this activity.

ASHP staff have no relevant financial relationships to disclose.

Executive Summary

Diabetes is a common illness with substantial morbidity and mortality and a large economic impact in the United States. Incretins are gastrointestinal hormones that promote pancreatic insulin secretion and suppress glucagon release after the ingestion of food. A diminished incretin effect in response to meals has been identified in patients with type 2 diabetes. Incretin agents—glucagon-like peptide-1 (GLP-1) receptor agonists and inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme that degrades GLP-1—were developed to overcome some of the limitations of older antidiabetic therapies. These two types of incretin agents differ from each other and older antidiabetic agents in several important ways, including adverse effects and cautions. The GLP-1 receptor agonists are given by injection, and their most common adverse effects are nausea and vomiting. The DPP-4 inhibitors are given orally and generally are well tolerated. The GLP-1 receptor agonists may cause weight loss, whereas DPP-4 inhibitors are weight neutral. Recent evidence-based guidelines for the treatment of adults with type 2 diabetes recommend the use of incretin agents primarily as part of combination therapy. Successful outcomes in patients with type 2 disease require an individualized treatment plan with glycemic goals and drug therapy based on patient characteristics, needs, preferences, and tolerances.

Introduction

Diabetes mellitus affects an estimated 25.8 million Americans or 8.3% of the U.S. population.[1] In 2012, the total cost of diagnosed diabetes in the United States was $245 billion, including $176 billion for direct medical costs and $69 billion in reduced productivity.[2] Most diabetes-related costs stem from macrovascular and microvascular complications. Diabetes is a major cause of heart disease and stroke and the leading cause of kidney failure, non-traumatic lower limb amputation, and new cases of blindness among American adults.[1] Diabetes is the seventh leading cause of death in the United States.[1] Type 2 disease accounts for 90% to 95% of diagnosed cases of diabetes.[1] It is characterized by insulin resistance and a progressive loss of pancreatic β-cell function, resulting in a relative insulin deficiency and subsequent hyperglycemia.[1]

Rationale for Developing Incretin Therapies

Type 2 diabetes is the result of defects in multiple organs, including the pancreas, liver, gastrointestinal (GI) tract, adipose tissues, skeletal muscle, brain, and kidneys.[3] No single antidiabetic drug therapy addresses all of the pathophysiologic defects associated with type 2 disease.[3] Therefore, combination therapy with complementary mechanisms of action that target multiple defects usually is required to provide glycemic control.[4,5]

The high morbidity and mortality from type 2 diabetes and shortcomings of older antidiabetic therapies (e.g., hypoglycemia, weight gain) have spurred research to further elucidate the pathogenesis of the disease and identify new therapeutic modalities. Roughly one in eight American adults with diabetes has poor glycemic control (A1c> 9%).[6]

Are administrators at your health care facility aware of the substantial morbidity, mortality, and financial burden of type 2 diabetes? How might you advocate for expanding your role in improving treatment outcomes in adults with this disease to minimize its economic impact?

Type 2 diabetes is a cardiometabolic disease, with alterations in glucose metabolism and vascular function that heighten cardiovascular risk.[7] Therapeutic goals include reducing cardiovascular morbidity and mortality as well as providing long-term glycemic control (i.e., a durable reduction in A1c) by slowing or stopping the decline in pancreatic β-cell function associated with the disease.[3]

Sulfonylureas have been used extensively to manage type 2 diabetes, but a risk for hypoglycemia and weight gain are disadvantages associated with this drug class (Table 1).[3,8,9,13] The long-term glucose-lowering effect of sulfonylureas usually is not durable, and these drugs do not provide cardiovascular benefits.[3,8]

Metformin also has been used extensively.[8] The risk of hypoglycemia from metformin is low. The drug does not cause weight gain, and it may result in a modest weight loss.[3] However, GI side effects often limit the metformin dosage tolerated.[11] The drug should not be used in patients with severe renal impairment, and a reduced dosage should be used for patients with moderate renal impairment.[12]

The risk of hypoglycemia from the thiazolidinedione pioglitazone is low.[3] A reduction in triglycerides and increase in high-density lipoprotein cholesterol, which may be beneficial in patients with diabetes and dyslipidemia, also are associated with pioglitazone.[4] However, weight gain, edema, heart failure, and distal extremity bone fractures (e.g., ankles, wrists) are potential problems with use of the drug.[3] A link between pioglitazone and bladder cancer has been suggested.[14] The thiazolidinedione rosiglitazone is rarely used because of concerns about an increased risk for myocardial infarction, although the issue is controversial.[8,15,16]

Roughly what percentage of the adult patients with type 2 diabetes at your health care facility achieve and maintain their glycemic goals? What are the typical characteristics of those patients who fail to do so? What antihyperglycemic therapies are they currently using? What therapeutic changes could be made to improve glycemic control and outcomes in these patients?

Insulin therapy improves glycemic control for all patients with type 2 diabetes.[10] It is particularly beneficial for patients who are symptomatic or have high A1c values or a long duration of disease.[13] However, the injectable route of administration and the risk for weight gain and hypoglycemia are disadvantages associated with insulin.[8]

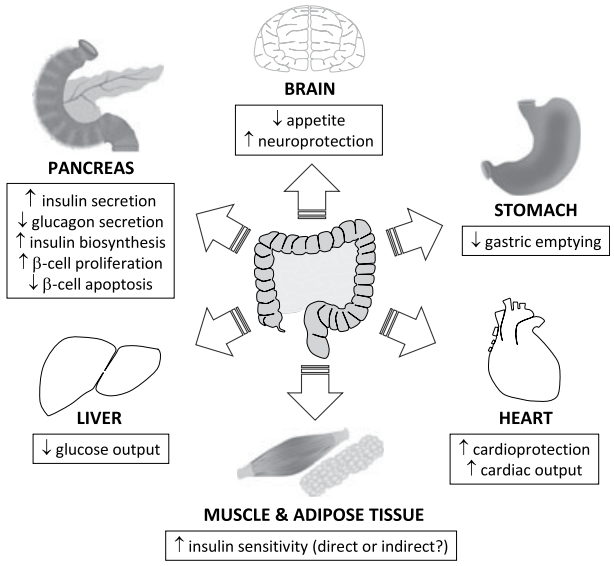
Pharmacology, Pharmacodynamics, and Safety of Incretin Agents

The incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are secreted by L cells and K cells, respectively, in the GI tract.[17] These GI hormones promote the secretion of insulin and suppress glucagon release by pancreatic β and α cells, respectively.[18] Most of the secretion of GLP-1 and GIP by L cells and K cells is glucose-dependent, increasing after the ingestion of food.[18,19]

In patients with newly-diagnosed type 2 diabetes mellitus and relatively good glycemic control (e.g., A1c <7%), secretion of GLP-1 and GIP in response to meals is comparable to that in persons without diabetes.[17] However, in patients with long-term type 2 diabetes and poor glycemic control (e.g., A1c 8% to 9%), GLP-1 secretion is diminished and GIP secretion is unchanged compared with healthy persons.[17] Although GLP-1 suppresses glucagon secretion by pancreatic α-cells, GIP lacks this effect.[20] Other physiologic effects of endogenous GLP-1 include increased satiety, slowed gastric emptying, and reduced hepatic glucose output (Figure 1).[3,18] Patients with type 2 diabetes

FIGURE 1

Physiologic Effects of Glucagon-Like Peptide-1



Reprinted with Permission from Reference 18.

TABLE 1

Pharmacology and Pharmacodynamics of Commonly Used Drug Therapies for Type 2 Diabetes[3,8-12]

Drug Class (Drug)	Site of Action	Primary Plasma Glucose Affected[a]	Potential Benefits and Advantages	Risks and Other Considerations
Biguanide (metformin)	Liver	FPG	Weight neutral or loss Low risk of hypoglycemia Low cost	GI side effects Need to reduce dosage in moderate renal impairment and avoid use in severe renal impairment
Sulfonylureas	Pancreas	FPG & PPG	Low cost	Weight gain Hypoglycemia Limited durability of long-term glycemic control
Thiazolidinedione (pioglitazone)	Liver, peripheral tissues (e.g. muscle), and fat	FPG & PPG	Low risk of hypoglycemia Reduces triglycerides, increases HDL-C	Weight gain Edema and heart failure Distal extremity bone fractures High cost Bladder cancer?
GLP-1 receptor agonists (exenatide, liraglutide)	GI tract, liver, pancreas, and brain	FPG (long-acting agents only[b]) & PPG (both long- and short-acting agents[c])	Weight loss Low risk for hypoglycemia	Injectable route of administration GI side effects Need for caution in renal insufficiency (see Table 3) High cost
DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin)	Liver and pancreas	PPG	Weight neutral Low risk for hypoglycemia Oral route of administration	Need for dosage reduction for all except linagliptin in moderate to severe renal impairment (see Table 3) High cost
Insulin	Liver, muscle, and fat	FPG (basal) or PPG (bolus)	Improves glycemic control for all patients Particularly useful for patients who are symptomatic or have high A1c or long duration of disease	Weight gain Hypoglycemia Injectable route of administration

CV = cardiovascular; DPP = dipeptidyl peptidase; FPG = fasting plasma glucose, GI = gastrointestinal; GLP = glucagon-like peptide; HDL-C = high-density lipoprotein cholesterol; PPG = postprandial plasma glucose

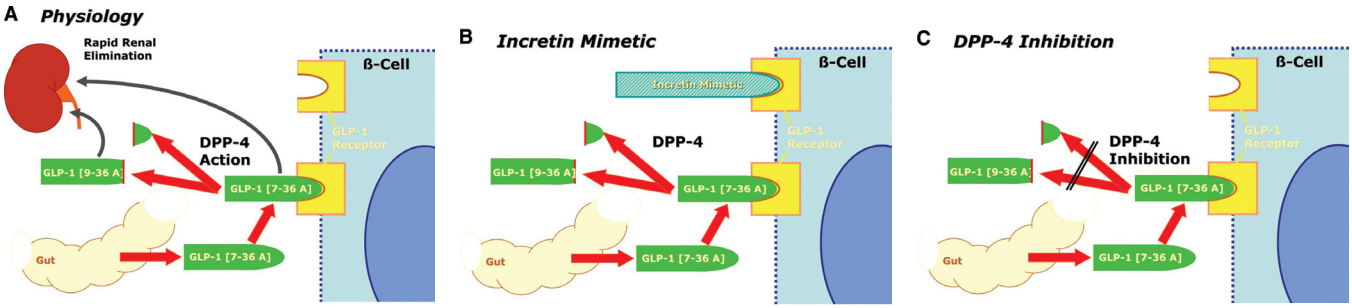
[a] The primary glucose affected does not reflect secondary effects. Lowering FPG can result in reduction of PPG. Lowering PPG can result in reduction of FPG.

[b] Long-acting GLP-1 receptor agonists include once-daily liraglutide and once-weekly exenatide (Bydureon).

[c] Short-acting GLP-1 receptor agonists include twice-daily exenatide (Byetta).

FIGURE 2

Mechanisms of Action of Incretin Therapies



Reference 21. Diabetes Care by American Diabetes Association. Reproduced with permission of American Diabetes Association in the format Continuing Education via Copyright Clearance Center.

and low GLP-1 plasma concentrations often have diminished insulin secretion, high postprandial glucagon levels, rapid gastric emptying, a tendency to overeat due to diminished satiety, and elevated plasma glucose concentrations compared with healthy individuals.[3] Therefore, GLP-1-based medications have been developed for the treatment of type 2 diabetes.

The enzyme dipeptidyl peptidase-4 (DPP-4) rapidly degrades and inactivates endogenous GLP-1 (Figure 2). The short half-life of GLP-1 (2 minutes) limits its therapeutic use.[21] The GLP-1 receptor agonists bind to and activate GLP-1 receptors, but these agents undergo little or no degradation by DPP-4 and are eliminated much more slowly than GLP-1.[21] DPP-4 inhibitors have been developed to suppress the majority (80% to 100%) of plasma DPP-4 enzyme activity, which increases endogenous plasma GLP-1 concentrations.[17,22]

The incretin agents do not cause hypoglycemia when the drugs are used alone because their effect on insulin secretion is glucose-dependent.[3] The GLP-1 receptor agonists differ from DPP-4 inhibitors in several important ways (Table 2).[21] The GLP-1 receptor agonists are given by subcutaneous (s.c.) injection, and the DPP-4 inhibitors are taken orally once daily with or without food (Table 3).

Treatment with GLP-1 receptor agonists produces pharmacologic concentrations of GLP-1 receptor activity that are 6- to 10-fold higher than the postprandial physiologic levels in persons without diabetes.[3] By contrast, DPP-4 inhibitors produce physiologic GLP-1 concentrations after meals in patients with type 2 diabetes that are similar to those in healthy individuals without diabetes.[3] This difference may result in a greater reduction in A1c

TABLE 2

Comparative Characteristics of Incretin Agents[3,8–11,21]

Characteristic	GLP-1 Receptor Agonists	DPP-4 Inhibitors
Route of administration	Subcutaneous injection	Oral
Effect on body weight	Weight loss	Weight neutral
Typical A1c reduction (%)	0.8–1.8	0.5–1.1
Risk for hypoglycemia	Low	Low
GI side effects	Yes[a]	No
Need for dosage reduction in renal insufficiency	No, although caution is needed in renal insufficiency (see Table 3)	Yes, except for linagliptin (see Table 3)
CV benefits	Possible, although not proven	Possible, although not proven
Cost	High	High

CV = cardiovascular; DPP = dipeptidyl peptidase; GI = gastrointestinal; GLP = glucagon-like peptide

[a] GI side effects from twice-daily exenatide and once-daily liraglutide are minimized by using a low initial dosage followed by gradual increases based on clinical response.

TABLE 3

Dosing and Administration of Incretin Agents[23–29]

Drug Class or Drug (Trade Name)	Dosage Form and Concentration or Strength	Route of Administration	Usual Dosage[a]	Use in Renal Impairment
SHORT-ACTING GLP-1 RECEPTOR AGONIST				
Exenatide (Byetta)	250-mcg/mL injection in 1.2-mL and 2.4-mL prefilled injector pens that deliver 5-mcg or 10-mcg doses (60 doses for a 30-day supply)	s.c. injection into abdomen, thigh or upper arm	5 mcg twice daily within 60 min before morning and evening meals (or before the two main meals of the day, approximately 6 hr or more apart); increased to 10 mcg twice daily after 1 month based on clinical response	*Moderate renal impairment (CrCl 30–50 mL/min)*: use caution when initiating therapy or escalating dosage *Renal transplantation:* use with caution *Severe renal impairment (CrCl <30 mL/min) or ESRD*: do not use drug
LONG-ACTING GLP-1 RECEPTOR AGONISTS				
Exenatide extended-release (Bydureon)	Vials with 2 mg exenatide as microspheres and prefilled syringes with 0.65 mL diluent for use in suspending and delivering the microspheres	s.c. injection into abdomen, thigh, or upper arm	2 mg once every 7 days at any time of day with or without meals	*Moderate renal impairment (CrCl 30–50 mL/min) or renal transplantation:* use with caution *Severe renal impairment (CrCl <30 mL/min) or ESRD*: do not use drug
Liraglutide (Victoza)	6-mg/mL injection in 3-mL prefilled injector pens that deliver 0.6-mg, 1.2-mg, or 1.8-mg doses	s.c. injection into abdomen, thigh, or upper arm	0.6 mg once daily at any time of day with or without meals for 1 week (to minimize GI symptoms, not provide glycemic control); increased to 1.2 mg once daily and if glycemic control is not acceptable, 1.8 mg once daily	Use caution when initiating therapy or escalating doses in patients with mild, moderate, or severe renal impairment, including ESRD
DPP-4 INHIBITORS				
Alogliptin (Nesina)	6.25-mg, 12.5-mg, and 25-mg tablets	Oral	25 mg once daily with or without food	*Mild renal impairment (CrCl ≥60 mL/min)*: no dosage reduction needed *Moderate renal impairment (CrCl 30–59 mL/min)*: 12.5 mg once daily *Severe renal impairment (CrCl <30 mL/min) or ESRD*: 6.25 mg once daily
Linagliptin (Tradjenta)	5-mg tablets	Oral	5 mg once daily with or without food	No dosage reduction needed
Saxagliptin *(Onglyza)*	2.5-mg and 5-mg tablets	Oral	2.5 mg or 5 mg once daily with or without food	*Moderate or severe renal impairment or ESRD (CrCl ≤50 mL/min):* 2.5 mg once daily
Sitagliptin (Januvia)	25-mg, 50-mg, and 100-mg tablets	Oral	100 mg once daily with or without food	*Mild renal impairment (CrCl >50 mL/min or SCr ≤1.7 mg/dL in men and ≤1.5 mg/dL in women):* no dosage reduction needed *Moderate renal impairment (CrCl 30-49 mL/min or SCr 1.8-3.0 mg/dL in men and 1.6-2.5 mg/dL in women):* 50 mg once daily *Severe renal impairment (SCr >3.0 mg/dL in men and >2.5 mg/dL in women) or ESRD*: 25 mg once daily

CrCl = creatinine clearance; DPP = dipeptidyl peptidase; ESRD = end-stage renal disease; GI = gastrointestinal; GLP = glucagon-like peptide; s.c. = subcutaneous; SCr = serum creatinine

[a]The dosages listed are those approved by the Food and Drug Administration for patients with normal renal function.

and higher risk of adverse effects from GLP-1 receptor agonists than DPP-4 inhibitors. In comparative clinical trials performed to date of patients with type 2 diabetes and inadequate glycemic control, the reductions from baseline in A1c achieved from GLP-1 receptor agonists were greater than those associated with DPP-4 inhibitors.[11,21] Significantly greater reductions in A1c were achieved from once-weekly exenatide or once-daily liraglutide (both of which are long-acting GLP-1 receptor agonists) than with twice-daily exenatide, which is a short-acting GLP-1 receptor agonist.[30–32] Differences in A1c reduction among the DPP-4 inhibitors appear to be small based on limited data, with similar reductions in A1c observed when the DPP-4 inhibitor sitagliptin or saxagliptin was combined with metformin.[33,34]

Most incretin agents affect postprandial plasma glucose (PPG) concentrations to a greater extent than fasting plasma glucose (FPG) concentrations.[21] Long-acting GLP-1 receptor agonists (i.e., once-weekly exenatide and once-daily liraglutide) address both FPG and PPG.[3]

The GLP-1 receptor agonists slow gastric emptying, which can delay postprandial nutrient absorption.[3] This delayed gastric emptying may result in nausea and vomiting. The central action of GLP-1 receptor agonists in the brain increases satiety, which can result in weight loss if caloric intake is reduced.[7] The DPP-4 inhibitors have minimal effects on gastric emptying and satiety. They are weight neutral and lack substantial GI adverse effects.[3] The nausea and vomiting from GLP-1 receptor agonists usually diminish over time.[23] Initiation of the GLP-1 receptor agonists liraglutide and twice-daily exenatide using small doses followed by gradual upward dosage titration based on clinical response reduces the severity of nausea.[23] Patients receiving these GLP-1 receptor agonists should be advised to stop eating when satiated (i.e., full or satisfied) to minimize vomiting. Dosage titration is not required when initiating DPP-4 inhibitors or extended-release (i.e., once-weekly) exenatide. Steady state plasma exenatide concentrations are reached slowly after 6–7 weeks of treatment with the extended-release form of the drug.[24]

Incretin agents could potentially provide cardiovascular benefits in patients with type 2 diabetes. Receptors for GLP-1 are found in the heart and blood vessels, and GLP-1 may play a role in modulating myocardial contractility, vascular tone, heart rate, and blood pressure.[18] However, the mechanisms involved in regulating heart rate and blood pressure are complex, making the impact of incretin therapy on these measures and cardiovascular events difficult to predict. Reductions in plasma concentrations of atherogenic lipids have been observed during incretin therapy in patients with type 2 diabetes.[3] Reductions in systolic blood pressure also have been associated with the use of GLP-1 receptor agonists in this patient population.[33] Because type 2 diabetes is a major risk factor for cardiovascular disease and an increased risk for cardiovascular events has been associated with some antidiabetic therapies (e.g., rosiglitazone), the Food and Drug Administration (FDA) established premarketing and postmarketing cardiovascular safety assessment requirements for new diabetes medications.[8] The results of two studies of the DPP-4 inhibitors alogliptin and saxagliptin conducted to fulfill these requirements recently were published.[35,36] In these placebo-controlled studies of patients with type 2 diabetes and a history of or increased risk for cardiovascular events, no increased risk for cardiovascular events was associated with the use of the DPP-4 inhibitors. Whether GLP-1 receptor agonists reduce the risk of cardiovascular events in patients with type 2 diabetes currently is under investigation.

The safety of incretin-based therapies is the subject of ongoing research. Postmarketing reports have been received of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, during treatment with incretin therapies.[23–29] However, analysis of large observational databases has not revealed an increased risk of pancreatitis from the use of incretin therapies compared with other antidiabetic therapies.[37] The potential risks and benefits of incretin therapy should be weighed before using these agents in patients with a history of pancreatitis. Type 2 diabetes is among the risk factors for acute pancreatitis (other risk factors include obesity, gallbladder disease, and hypertriglyceridemia).[38] Patients initiating incretin therapy should be observed closely for and asked to report signs and symptoms of pancreatitis (e.g., severe abdominal pain radiating to the back, with or without vomiting). Therapy should be discontinued promptly if pancreatitis is suspected.

Concerns have been raised about the possibility that incretin therapies could increase the risk for pancreatic cancer because chronic pancreatitis and diabetes are risk factors for this malignancy.[39,40] The currently available evidence suggests that there probably is no increased risk for pancreatic cancer from incretin therapies, although additional research is needed.

Benign and malignant thyroid C-cell tumors have been detected in studies of some but not all types of animals exposed to liraglutide and extended-release (i.e., once-weekly) exenatide.[24,25] The relevance of these findings for humans receiving these drugs is unknown. Nevertheless, liraglutide and extended-release exenatide should not be used in patients with a personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome type 2.[24,25] Patients receiving these drugs should be advised to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, dyspnea).

Postmarketing reports have been received of acute renal failure, sometimes requiring hemodialysis or kidney transplantation, in patients receiving GLP-1 receptor agonists and some DPP-4 inhibitors, although causality has not been established for DPP-4 inhibitors.[23–25,27,29] Acute renal failure in patients receiving GLP-1 receptor agonists is probably the result of the nausea, vomiting, and reduced oral fluid intake associated with use of these agents. Neither the twice-daily nor the once-weekly form of exenatide should be used in patients with severe renal impairment or end-stage renal disease (ESRD), and the drugs should be used with caution in patients with renal transplantation or moderate renal impairment (Table 3) because exenatide is metabolized and cleared by the kidneys.[23,24,41] Liraglutide should be used with caution when initiating therapy or escalating the dosage in patients with mild, moderate, or severe renal impairment, including ESRD.[25] No liraglutide dosage adjustment is needed for these patients.[25] A reduction in dosage of all DPP-4 inhibitors except linagliptin is recommended for patients with moderate or severe renal impairment (Table 3). The kidneys play an important role in elimination of most DPP-4 inhibitors (the role of the kidneys in linagliptin elimination is minimal). However, dosage reductions in patients with renal impairment are recommended primarily to limit exposure to the drug and the risk of adverse effects that have not yet been detected, not because of concerns about nephrotoxicity. Exposure to plasma DPP-4 inhibitor concentrations in excess of those that provide 100% inhibition of plasma DPP-4 enzymes is unnecessary.

Postmarketing reports have been received about fatal and nonfatal hepatic failure in patients taking alogliptin.[26] Hepatotoxicity has not been reported in patients taking other DPP-4 inhibitors or GLP-1 receptor agonists.[42] A causal role between the use of alogliptin and hepatic failure has not been established. Nevertheless, a standard liver function test is recommended before initiating alogliptin therapy. The drug should be used with caution in patients with abnormal liver function. Patients receiving alogliptin should be advised to report symptoms of liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, and jaundice. Alogliptin therapy should be interrupted if clinically significant liver enzyme elevations develop.

Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been received in patients receiving incretin agents.[23–26,28,29] Therapy should be discontinued promptly and supportive care should be provided if hypersensitivity develops.

Place of Incretin Therapy in Type 2 Diabetes

Metformin is considered first-line therapy for type 2 diabetes unless it is contraindicated or not tolerated.[43] Evidence-based guidelines from most authoritative groups recommend incretin therapies in combination with other antidiabetic agents as second-line therapy after metformin plus lifestyle modifications (i.e., diet, exercise) have failed to provide adequate glycemic control in patients with type 2 diabetes.[8,43] Lifelong diet and exercise are recommended for patients with type 2 diabetes.

In adults with type 2 diabetes, metformin alone provides a greater reduction in A1c than DPP-4 inhibitors alone, and metformin plus DPP-4 inhibitors are more effective for reducing A1c than metformin alone.[44] Patients who are symptomatic or have high A1c levels or a long duration of disease may require insulin with or without additional agents as initial therapy.[43]

The 2012 position statement of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) calls for metformin as initial drug therapy with the addition of a sulfonylurea, thiazolidinedione, GLP-1 receptor agonist, DPP-4 inhibitor, or insulin (usually basal) if the target A1c has not been achieved and maintained after 3 months of metformin monotherapy.[8] A three-drug combination using metformin and a sulfonylurea, thiazolidinedione, GLP-1 receptor agonist, DPP-4 inhibitor, or insulin is recommended if the target A1c is not achieved after 3 months of dual therapy (Table 4).[8] When a GLP-1 receptor agonist or DPP-4 inhibitor is used as part of triple therapy, it is used with metformin and a sulfonylurea, thiazolidinedione, or insulin. Use of both a GLP-1 receptor antagonist and DPP-4 inhibitor as part of

TABLE 4

General Recommendations from the ADA and EASD for Antihyperglycemic Therapy in Patients with Type 2 Diabetes[8,a]

INITIAL THERAPY

Metformin + lifestyle modifications[b] for 3 months

IF INITIAL THERAPY FOR 3 MONTHS IS INADEQUATE

Dual therapy with metformin, lifestyle modifications[b], and one of the following:

SU	TZD	GLP-1 receptor agonist	DPP-4 inhibitor	Insulin (usually basal)

IF DUAL THERAPY FOR 3 MONTHS IS INADEQUATE

Triple therapy with metformin, lifestyle modifications[b], and:

SU plus one of the following:	**TZD** plus one of the following:	**GLP-1 receptor agonist** plus one of the following:	**DPP-4 inhibitor** plus one of the following:	**Insulin** (usually basal) plus one of the following:
TZD	SU	SU	SU	TZD
GLP-1 receptor agonist	GLP-1 receptor agonist	TZD	TZD	GLP-1 receptor agonist
DPP-4 inhibitor	DPP-4 inhibitor	Insulin	Insulin	DPP-4 inhibitor

COMPLEX STRATEGIES with multiple daily insulin doses, usually in combination with one or two non-insulin agents[a] and lifestyle modifications[b]

ADA = American Diabetes Association; DPP = dipeptidyl peptidase; EASD = European Association for the Study of Diabetes; GLP = glucagon-like peptide; SU = sulfonylurea; TZD = thiazolidinedione

[a] Adapted from a position statement of the American Diabetes Association and European Association for the Study of Diabetes on the management of hyperglycemia in type 2 diabetes: a patient-centered approach. Therapy should progress from the top to the bottom of table based on therapeutic response (i.e., A1c), although the complex strategies listed at the bottom of the table may be used as initial therapy for patients presenting with severe hyperglycemia or an A1c of 10.0% to 12.0%, with or without catabolic features (weight loss, ketosis).

[b] Lifestyle modifications include healthy eating, weight control, and increased physical activity.

triple therapy currently is not recommended. More complex strategies (e.g., multiple daily insulin doses in combination with one or two non-insulin agents) may be needed if triple therapy that includes basal insulin is not effective for providing glycemic control within 3–6 months.

In a 2013 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) algorithm for glycemic control in patients with type 2 diabetes, treatment is based on the initial A1c level.[5] In patients with an initial A1c less than 7.5%, monotherapy with metformin, a GLP-1 receptor agonist, DPP-4 inhibitor, or α-glucosidase inhibitor (e.g., acarbose, miglitol) is recommended in that order of preference. If the A1c remains above 6.5% after 3 months of monotherapy, dual therapy is recommended followed by triple therapy if glycemic control is not achieved within 3 months after addition of a second agent.

Combination therapy using agents with complementary mechanisms of action is needed for most patients with an initial A1c of 7.5% or higher.[5] Dual therapy is recommended by AACE/ACE as initial therapy for patients with an A1c of 7.5% to 9.0%, and a GLP-1 receptor agonist or DPP-4 inhibitor (in that order of preference) may be used in combination with metformin for this dual therapy.

In patients with an initial A1c exceeding 9.0%, dual or triple therapy is recommended in the AACE/ACE algorithm if the patient is asymptomatic.[5] A GLP-1 receptor agonist or DPP-4 inhibitor may be used as part of these regimens, although the two types of incretin therapy should not be used together. Insulin therapy with or without other agents is recommended for patients with an initial A1c higher than 9.0% who are symptomatic and patients who are asymptomatic and unable to meet their A1c goal despite the use of non-insulin therapy.

Tailoring Drug Therapy to Individual Patients

Individualization of treatment for type 2 diabetes is the cornerstone of success.[8] Patient needs, preferences, and tolerances should be taken into consideration in developing a treatment plan. A target A1c less than 7% is recommended for most patients by the ADA, and 6.5% or less is recommended by the AACE.[4,43] Considerations in establishing glycemic goals include the duration of diabetes, life expectancy, the presence of diabetes complications and extensive comorbid conditions, and concerns about hypoglycemia or other adverse effects from drug therapy.[43] The duration of diabetes is a consideration because β-cell function deteriorates as the disease progresses.[3] Although a target A1c of less than 7% is chosen for most patients, a more lenient target (e.g., 8% or lower) might be chosen for patients with a long history of diabetes, short life expectancy, advanced diabetes complications or extensive comorbid conditions, unstable cardiac disease, or a recent history of severe hypoglycemia.[8] Conversely, a more stringent target of 6.5% or less might be chosen for patients with a short history of diabetes, long life expectancy, and no diabetes complications, comorbid conditions, or history of severe hypoglycemia.[8] The patient's self-care abilities and motivation should be evaluated because lower glycemic goals may be feasible for high functioning individuals whereas a higher goal may be required for less motivated persons with poor self-care abilities.[5] The need to individualize glycemic goals should not be used as an excuse for poor glycemic control. Appropriate individualization of goals can lower the risk of complications while avoiding harm from drug therapy.

Other patient characteristics and concerns that should be taken into consideration in selecting drug therapy for type 2 diabetes include (1) which plasma glucose needs to be addressed (i.e., FPG, PPG, or both), (2) the magnitude of A1c lowering required (if it exceeds 2%, insulin or dual or triple drug therapy probably is needed), and (3) the presence of obesity, overweight, cardiovascular disease, and renal impairment.[3] The potential benefits and risks associated with commonly-used drug therapies listed in Table 1 can facilitate the decision-making process. Drug therapies associated with weight loss or a weight neutral effect often are preferred for patients who are obese or overweight. Drug therapies that may provide cardiovascular benefits usually are preferred over those with no such benefits (e.g., sulfonylureas) in patients with cardiovascular disease.

What can you do as a health care professional to ensure that incretin agents are used properly to optimize glycemic control in patients with type 2 diabetes at your health care facility? Why do you think GLP-1 receptor agonists are not used more widely at your facility despite the available evidence supporting their benefits? Could DPP-4 inhibitors be used more in your special populations, such as elderly patients?

Patient tolerability of side effects, especially GI side effects and hypoglycemia, should be taken into consideration when selecting drug therapy.[8] Avoidance of severe hypoglycemia should be a priority. Patient preference for route of administration, dosing frequency, and cost may be important concerns. If the patient will not obtain, administer, or adhere to drug therapy, the likelihood of therapeutic success is greatly diminished.

The low risk of hypoglycemia and weight gain from incretin agents make these drugs useful for a wide variety of patient populations. Because DPP-4 inhibitors are taken orally once daily, weight neutral, and well tolerated, they may be particularly helpful for elderly patients and patients with GI side effects from other antidiabetic agents.[13] Obese or overweight patients could benefit more from GLP-1 receptor agonists than DPP-4 inhibitors because of the potential for weight loss associated with GLP-1 receptor agonists, although injection is required.[13] Greater patient satisfaction has been reported from GLP-1 receptor agonists than DPP-4 inhibitors despite GI side effects and the need for injection, possibly because of greater satiety, weight loss, and efficacy in reducing A1c.[33] The high cost of the drugs are considerations in the use of all incretin agents.

Conclusion

Diabetes has a large clinical and economic impact in the United States. Incretin agents may play an important role in improving outcomes in adults with type 2 diabetes. An individualized approach to decision making about the treatment plan is needed to optimize patient outcomes.

Continuing Education Credit Information

To Receive Continuing Education Credit

Once you have read the discussion guide (an assessment test is provided below as a study aid only), click on the link below to take the online assessment test (minimum score 70%) and complete your evaluation. Participants may print their official statements of continuing education credit immediately.

Take Test & Process CE

Accreditation for Pharmacists

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.10 CEU) of continuing pharmacy education credit (ACPE activity #0204-0000-14-469-H01-P).

Accreditation for Nurses

Educational Review Systems is an approved provider of continuing nursing education by the Alabama State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation (provider #5-115).

Accreditation for Nurse Practitioners

This program is approved for 1.0 contact hour of continuing education (which includes 1.0 hour of pharmacology) by the American Association of Nurse Practitioners. Program ID 1401007. This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Assessment Test Study Aid

This assessment test is provided here as a study aid only. Follow the instructions on the previous page to complete this assessment test and the evaluation online to obtain CE credit for this activity.

1. **Which of the following is a disadvantage associated with the use of pioglitazone to treat type 2 diabetes in adults?**
   a. Need for dosage reduction in renal impairment
   b. GI side effects
   c. Hypoglycemia
   d. Weight gain

2. **Which of the following is a physiologic effect of endogenous GLP-1 in persons without type 2 diabetes?**
   a. Increased gastric emptying
   b. Increased glucagon secretion
   c. Increased hepatic glucose output
   d. Increased satiety

3. **Incretin agents are unlikely to cause hypoglycemia because:**
   a. They do not act on the pancreas
   b. They do not affect β-cell function
   c. Their effects are glucose-dependent
   d. Their effects are insulin-dependent

4. **Which of the following best explains the higher risk of GI adverse effects from GLP-1 receptor agonists compared with DPP-4 inhibitors?**
   a. Greater reduction in A1c from GLP-1 receptor agonists
   b. Injectable instead of oral route of administration of GLP-1 receptor agonists
   c. Higher (i.e., pharmacologic) concentrations of GLP-1 receptor activity after meals from GLP-1 receptor agonists
   d. Higher (i.e., physiologic) concentrations of GLP-1 after meals from DPP-4 inhibitors

5. **Which of the following DPP-4 inhibitors does NOT require dosage adjustment for a patient with moderate renal impairment (creatinine clearance 35 mL/min)?**
   a. Linagliptin
   b. Alogliptin
   c. Saxagliptin
   d. Sitagliptin

6. **Most DPP-4 inhibitors require a reduction in dosage in patients with moderate or severe renal impairment because of concerns about:**
   a. Nephrotoxicity
   b. Undetected adverse effects
   c. Acute pancreatitis
   d. Hepatotoxicity

7. **Which of the following incretin agents should be avoided in a patient with type 2 diabetes and a personal or family history of medullary thyroid carcinoma?**
   a. Twice-daily exenatide
   b. Liraglutide
   c. Alogliptin
   d. Saxagliptin

8. **Which of the following target A1c values is optimal for a 55-year-old patient with recently diagnosed type 2 diabetes and no evidence of diabetes complications or comorbid conditions?**
   a. 6.5% or lower
   b. 7% or lower
   c. 8% or lower
   d. 9% or lower

9. **Which of the following types of adult patients with type 2 diabetes is most likely to require insulin as part of initial diabetes therapy?**
   a. Patients with a short life expectancy
   b. Patients with cardiovascular disease
   c. Patients who are symptomatic
   d. Patients with a recent history of severe hypoglycemia

10. **In an obese adult with type 2 diabetes, hypertension, and an A1c of 8% despite 3 months of metformin monotherapy and lifestyle modifications, which of the following types of antidiabetic agents is the best choice to add?**
   a. A DPP-4 inhibitor
   b. A GLP-1 receptor agonist
   c. A sulfonylurea
   d. A thiazolidinedione

11. **Which of the following adult patient populations with type 2 diabetes is most likely to benefit from the use of DPP-4 inhibitors instead of GLP-1 receptor agonists?**
   a. Obese patients
   b. Patients with a recent history of severe hypoglycemia
   c. Patients with cardiovascular disease
   d. Patients who prefer to avoid injections

12. **Which of the following is most likely to present a concern in using a DPP-4 inhibitor for an elderly woman with type 2 diabetes who is 5'2" tall, weighs 85 kg, is vision impaired, lives on a fixed income in a retirement home, and experienced problematic GI side effects from metformin?**
   a. Preference to avoid injections
   b. Potential for GI side effects
   c. Obesity
   d. High cost

References

1. Centers for Disease Control and Prevention. National diabetes fact sheet, 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf (accessed 2013 Nov 22).
2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care.* 2013; 36:1033–46. Available at: http://care.diabetesjournals.org/content/36/4/1033.full.pdf+html.
3. Cornell S, Dorsey VJ. Diabetes pharmacotherapy in 2012: considerations in medication selection. *Postgrad Med.* 2012; 124:84–94.
4. Handelsman Y, Mechanick JI, Blonde L et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract.* 2011; 17(suppl 2):1–53. Available at: www.aace.com/files/dm-guidelines-ccp.pdf.
5. Garber AJ, Abrahamson MJ, Barzilay JI et al. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract.* 2013; 19:327–36. Available at: www.aace.com/files/aace_algorithm.pdf.
6. Ali MK, McKeever Bullard K, Imperatore G et al. Characteristics associated with poor glycemic control among adults with self-reported diagnosed diabetes—National Health and Nutrition Examination Survey, United States, 2007–2010. *MMWR Morb Mortal Wkly Rep.* 2012; 61(suppl):32–7. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/su6102a6.htm#tab.
7. Schwartz S, Kohl BA. Type 2 diabetes mellitus and the cardiometabolic syndrome: impact of incretin-based therapies. *Diabetes Metab Syndr Obes.* 2010; 3:227–42.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012; 35:1364–79. Available at: http://care.diabetesjournals.org/content/early/2012/04/17/dc12-0413.full.pdf+html.
9. Rodbard HW, Jellinger PS, Davidson JA et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract.* 2009; 15:540–59.
10. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2009; 32:193–203.
11. Unger J, Parkin CG. Type 2 diabetes: an expanded view of pathophysiology and therapy. *Postgrad Med.* 2010; 122: 145–57.
12. Lipska, KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care.* 2011; 34:1431–7.
13. Triplitt C. Improving treatment success rates for type 2 diabetes: recommendations for a changing environment. *Am J Manag Care.* 2010; 16(7 suppl):S195–200.
14. Lewis JD, Ferrara A, Peng T et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care.* 2011; 34:916–22.
15. Avandia (rosiglitazone) prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2013 Sep.
16. U.S. Food and Drug Administration. FDA drug safety communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. November 25, 2013. www.fda.gov/Drugs/DrugSafety/ucm376389.htm (accessed 2013 Dec 4).
17. Chia CW, Egan JM. Incretin-based therapies in type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2008; 93:3703–16.
18. Grieve DJ, Cassidy RS, Green BD. Emerging cardiovascular actions of the incretin hormone glucagon-like peptide-1: potential therapeutic benefits beyond glycaemic control? *Br J Pharmacol.* 2009; 157:1340–51.
19. Triplitt CL. Examining the mechanisms of glucose regulation. *Am J Manag Care.* 2012; 18:S4–S10.
20. Freeman JS. The pathophysiologic role of incretins. *J Am Osteopath Assoc.* 2007; 107(suppl):S6-9. Available at: www.jaoa.org/content/107/suppl_3/S6.full.pdf.
21. Nauck MA, Vilsboll T, Gallwitz B et al. Incretin-based therapies: viewpoints on the way to consensus. *Diabetes Care.* 2009; 32(suppl 2):S223–31.
22. Ahren B. Dipeptidyl peptidase-4 inhibitors: clinical data and clinical implications. *Diabetes Care.* 2007; 30:1344–50.
23. Byetta (exenatide) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2013 Feb.
24. Bydureon (exenatide extended-release) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2013 Feb.
25. Victoza (liraglutide) prescribing information. Plainsboro, NJ: Novo Nordisk Inc; 2013 Apr.
26. Nesina (alogliptin) prescribing information. Deerfield, IL: Takeda Pharmaceuticals America, Inc: 2013 Jan.
27. Tradjenta (linagliptin) prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2013 Jun.
28. Onglyza (saxagliptin) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2013 May.
29. Januvia (sitagliptin) prescribing information. Whitehouse Station, NJ: Merck & Co., Inc; 2013 Aug.

30. Drucker DJ, Buse JB, Taylor K et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet.* 2008; 372:1240–50.

31. Blevins T, Pullman J, Malloy J et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2011; 96:1301–10.

32. Buse JB, Rosenstock J, Sesti G et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet.* 2009; 374:39–47.

33. Russell S. Incretin-based therapies for type 2 diabetes mellitus: a review of direct comparisons of efficacy, safety and patient satisfaction. *Int J Clin Pharm.* 2013; 35:159–72.

34. Scheen AJ, Charpentier G, Ostgren CJ et al. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev.* 2010; 26:540–9.

35. White WB, Cannon CP, Heller SR et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013; 369:1327–35.

36. Scirica BM, Bhatt DL, Braunwald E et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013; 369:1317–26.

37. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care.* 2010; 33:2349–54.

38. Lai SW, Muo CH, Liao KF et al. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. *Am J Gastroenterol.* 2011; 106:1697–704.

39. Butler PC, Dry S, Elashoff R. GLP-1-based therapy for diabetes: what you do not know can hurt you. *Diabetes Care.* 2010; 33:453–5.

40. Andersen DK, Andren-Sandberg A, Duell EJ et al. Pancreatitis-diabetes-pancreatic cancer: summary of an NIDDK-NCI workshop. *Pancreas*. 2013; 42:1227–37.

41. U.S. Food and Drug Administration. Information for healthcare professionals: reports of altered kidney function in patients using exenatide (marketed as Byetta). November 2, 2009. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm188656.htm (accessed 2013 Nov 22).

42. National Institute of Diabetes and Digestive and Kidney Diseases. Drug record: dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors). November 5, 2013. http://livertox.nlm.nih.gov/DipeptidylPeptidase4Inhibitors.htm (accessed 2013 Nov 22).

43. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care.* 2013; 36(suppl 1): S11–66.

44. Bennett WL, Wilson LM, Bolen S et al. Oral diabetes medications for adults with type 2 diabetes: an update [Internet]. (Comparative Effectiveness Reviews, No. 27.) Rockville, MD: Agency for Healthcare Research and Quality; March 2011. www.ncbi.nlm.nih.gov/books/NBK55748/ (accessed 2013 Nov 22).