JMCP

JOURNAL OF MANAGED CARE PHARMACY®

What Are Incretins, and How Will They Influence the Management of Type 2 Diabetes?

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Supplement

September 2006

Vol. 12, No. 7, S-a

Continuing Education Program

JMCP

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This supplement to the Journal of Managed Care Pharmacy (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; (703) 683-8416; (703) 683-8417 (fax).

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POSTMASTER: Send address changes to JMCP, 100 North Pitt St., Suite 400, Alexandria, VA 22314.

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FACULTY

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Blonde is chair of the Steering Committee of the National Diabetes Education Program, a partnership of the National Institutes of Health, the Centers for Disease Control and Prevention, and more than 200 public and private organizations working to "change the way diabetes is treated." A member of the Board of Directors of the American Association of Clinical Endocrinologists (AACE), he also serves on the Board of Directors of the Council for the Advancement of Diabetes Research and Education (CADRE) and is a member of the National Quality Forum Adult Diabetes Care Consensus Maintenance Committee. Blonde is chair of the American Diabetes Association (ADA) Doing Better Committee and a former member of the ADA board of directors. He is a current member and former chair of the ADA Professional Practice Committee, which develops practice guidelines for the care of people with diabetes.

He has served on the Microsoft Health Care Users Group Board of Directors and as a member of the Residency Review Committee for Internal Medicine and the Transitional Review Committee of the Accreditation Council for Graduate Medical Education. Blonde has also been a member of the Council of the Association of Program Directors in Internal Medicine, the Council of the Association of Subspecialty Professors, and the ACP Medical Informatics Subcommittee, for which he served as chair.

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Active in clinical research, Rosenstock has published more than 80 articles and 80 abstracts and contributed to 10 book chapters on various topics in the field of diabetes, including hypertension in diabetes, diabetic neuropathy, nephropathy and glycemic control, blood glucose and genetic susceptibility, monotherapy and combination therapy in the treatment of diabetes, insulin therapy, nocturnal hypoglycemia, and management of diabetes in the elderly. His clinical and research activities have focused on intensive diabetes management strategies and novel therapies to improve glycemic control to prevent and retard diabetes complications. His work has appeared in such journals as *Diabetes Care*; *JAMA*; *Lancet*; *Annals of Internal Medicine*; *Diabetes*, *Obesity*, and *Metabolism*; and *The American Journal of Medicine*. Rosenstock served as a member of the editorial board of *Clinical Diabetes and Endocrine Practice*. He currently serves on the editorial boards of *Practical Diabetology*, *The Journal of the HispanoAmerican Biomedical Association*, and *Cardiovascular Diabetology*.

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Triplitt is an investigator in multiple research studies in the field of diabetes, clinically manages and educates people with diabetes with an endocrinologist, and is a certified diabetes educator. He also has been involved with the development of multiple clinical treatment algorithms for the Texas Diabetes Council, which spearheads a statewide effort to improve care for people with diabetes.

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Lawrence Blonde, MD, FACP, FACE; Julio Rosenstock, MD; and Curtis Triplitt, PharmD, CDE, BCPS

S13 Continuing Education*:

CE Submission Instructions and Posttest

Target Audience

Managed care pharmacists and other health care professionals, including pharmacy directors and medical directors, who are involved in the treatment of type 2 diabetes

Learning Objectives

Upon completion of this activity, the participant will be better able to

1. identify the percentage of T2DM patients who fail to reach therapeutic goals and the impact of this failure on cost, quality of life, and complication rates;
2. review the often-overlooked aspects of diabetes pathophysiology, including the role incretins play in the processes that contribute to glucose homeostasis;
3. review incretin-based therapeutic options, including GLP-1 analogues, GLP-1 agonists, and DPP-4 inhibitors and understand their roles in current and potential future treatment regimens; and
4. discuss the potential pharmacoeconomic implications of incretin-based therapies in the managed care setting.

This supplement was funded by an unrestricted educational grant from Novartis Pharmaceuticals Corporation and sponsored by Medical Education Resources and Consensus Medical Communications. The article in this supplement is based on the proceedings of a symposium, "What Are Incretins, and How Will They Influence the Management of Type 2 Diabetes?" held April 7, 2006, at the Academy of Managed Care Pharmacy's 18th Annual Meeting and Showcase in Seattle, Washington, which was supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation and sponsored by Medical Education Resources and Consensus Medical Communications.

*A total of 0.15 CEU (1.5 contact hours) will be awarded for successful completion of this continuing education program (ACPE Program No. 816-999-06-003-H01). For faculty disclosures, please see page S11. For ACPE accreditation information, please see page S14.

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What Are Incretins, and How Will They Influence the Management of Type 2 Diabetes?

LAWRENCE BLONDE, MD, FACP, FACE; JULIO ROSENSTOCK, MD; and CURTIS TRIPLITT, PharmD, CDE, BCPS

ABSTRACT

OBJECTIVE: To review the pathophysiology of type 2 diabetes (T2DM), the role of incretins, the potential of incretin-based therapies to address unmet therapeutic needs in T2DM, and the potential impact this will have on the contribution of managed care pharmacy to diabetes therapy.

SUMMARY: Diabetes, the fifth leading cause of death by disease in the United States, costs approximately \$132 billion per year in direct and indirect medical expenses. According to the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey, a majority of diabetes patients do not achieve target A1C levels with their current treatment regimens. Advances in understanding the pathophysiologic abnormalities underlying the metabolic dysfunctions associated with T2DM are leading to the development of new treatment approaches and new therapeutic classes of drugs. Novel incretin-based therapies currently available, and in late-stage development, are among those showing the greatest promise for addressing the unmet needs of traditional therapies.

KEYWORDS: Type 2 diabetes, Incretin, GLP-1, DPP-4. Managed care

J Manag Care Pharm. 2006;12(7)(suppl S-a):S2-S12

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Despite the overwhelming evidence that improved glycemic control will reduce diabetic complications, almost 60% of diabetes patients fail to meet even the minimum A1C goal of <7%.¹ The economic impact of diabetes is extensive. In the United States, total expenditures attributable to diabetes rose from \$98 billion in 1997 to \$132 billion in 2002. Direct medical costs alone more than doubled, from \$44 billion to \$91.8 billion in the same period.²

While it is widely recognized that β -cell dysfunction and reduction of β -cell mass contribute to the pathophysiology of T2DM, α -cell dysregulation also occurs and the resulting increased levels of glucagon contribute to diabetic hyperglycemia, especially in the postprandial period. Conventional therapy fails to adequately address some of these components of pathophysiology. Recent research has focused on the role of incretins in the maintenance of glucose homeostasis through their actions on both α - and β -cell function and their potential roles in β -cell growth and development. This research has led to the development of new therapeutic agents for the treatment of T2DM, including injectable glucagon-like peptide-1 (GLP-1) analogues, GLP-1 agonists, and oral dipeptidyl peptidase-4 (DPP-4) inhibitors.

This paper will briefly review the epidemiology and overall economic burden of T2DM, the disease pathophysiology, and conventional T2DM therapies and their ability to achieve glycemic control. It will describe the role of incretins in glucose homeostasis and T2DM as well as introduce the potential for new incretin-related therapies to address currently unmet needs. The effect of these new treatment options on managed care pharmacy will also be discussed.

Obesity and Diabetes on the Rise

In 1994, only 7 states in the United States had obesity prevalence rates as high as 15% to 19%. By 2004, this "low" rate was seen in only 3 states, with the rest of the country exhibiting obesity rates of at least 20% to 24% and 9 states classifying more than 25% of their populations as obese (defined as body-mass index [BMI] ≥ 30 or excess weight of at least 30 pounds on a person who is 5'4").³ There is a strong association between obesity and T2DM (approximately 50% of people with diabetes are classified as obese),⁴ and from 1994 to 2004, diabetes prevalence rates also dramatically increased nationwide. By 2004, most states reported that more than 6% of their populations had the disease (Figure 1).

The problem of diabetes is likely to get worse before it gets better as young, overweight, and obese persons carry their elevated risk of morbidity and mortality into middle age and beyond. A recent *New England Journal of Medicine* article predicts that because of obesity's negative impact on longevity, the present generation of children and adolescents may be the first in U.S. history to experience shorter lifespans than their parents.

Prevalence and Economics

In 2005, an estimated 20.8 million Americans (7% of the U.S. population) had diabetes, a 70% increase in just 5 years from the estimate of 12 million in 2000.^{6,7} About 95% of the current diabetes patient population is diagnosed with T2DM, and it is estimated that there are an additional 41 million people with prediabetes.⁷

The effects of diabetes can have a life-long impact on patients. In the short term, hyperglycemia and its associated effects on body processes impair how diabetes patients feel and function. In the longer term, diabetes frequently results in both macrovascular and microvascular complications. Among adults with diabetes, the rate of death from heart disease and the risk of stroke are each 2 to 4 times higher than those without diabetes. Diabetes is the leading cause of adult blindness, nontraumatic amputation, and end-stage renal disease (ESRD) in the United States, accounting for 44% of new cases of ESRD in 2003.⁸ As reflected in Table 1,^{2,7} the cardiovascular complications of diabetes result in 77,000 deaths annually.

Largely because of these complications, diabetes exacts great personal and societal costs. An American Diabetes Association (ADA) study estimated that, in 2002, the combined direct and indirect expenditures attributable to diabetes in the United States were \$132 billion.² Of this, about \$92 billion was related to the direct medical costs of hospitalization, medication, and outpatient care (Table 1). Indirect and other costs, including disability, loss of work, and premature mortality, accounted for the other \$40 billion.^{2,7,9} The direct costs of all diabetes medications and supplies constitute the smallest portion of the total expense (\$17.5 billion, or 13%), and outpatient care (\$20.1 billion) represents a minority of these expenditures. Indeed, one might argue that devoting more resources to medications, supplies, and outpatient therapy might actually save costs by reducing complications and associated hospitalization and indirect costs. Further details on the economic toll of diabetes are provided later in this monograph.

Goals for Disease Management

The core of any diabetes management strategy is the control of blood glucose. The ADA goal for patients in general is an A1C of <7%. However, the goal for an individual patient is an A1C as close to normal (<6%) as possible without significant hypoglycemia. The American College of Endocrinology (ACE) goal is ≤6.5%. Other management goals from the ADA include the following:

- blood pressure <130/80 mmHg
- lipid levels, including low-density lipoprotein cholesterol (LDL-C) levels of <100 mg/dL generally, with a lower goal of <70 mg/dL in the presence of cardiovascular disease; high-density lipoprotein cholesterol levels of >40 mg/dL in men and >50 mg/dL in women; and total triglyceride levels of <150 mg/dL
- aspirin regimen (75-162 mg/day) in adult patients with

FIGURE 1 The Prevalence of Obesity* and Diabetes Continues to Increase

*Obesity defined as BMI ≥30 or ~30 pounds overweight for a 5'4" person. Behavioral Risk Factor Surveillance System, Centers for Disease Control and Prevention. Available at: www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/ and www.cdc.gov/diabetes/statistics/prev/state/. Accessed January 20, 2006. BMI=body mass index.

TABLE 1 Economic and Health-Related Costs Associated With Diabetes^{2,7}

Inpatient care	\$54.2 billion
Outpatient care	\$20.1 billion
Medication and supplies	\$17.5 billion
Indirect costs	\$39.8 billion
Total	\$131.6 billion
Morbidity and Mortality	
Cardiovascular disease	77,000 deaths/year
Blindness	12,000 to 24,000 newly blind people/year
Kidney disease	27,000 people with kidney disease/year
Neuropathy	82,000 amputations/year

diabetes and macrovascular disease or for primary prevention in patients older than 40 years with diabetes or more than one other cardiovascular risk factor

- smoking cessation¹⁰

Complications and Control

There is strong evidence from prospective randomized trials of the benefits of improved glycemic control, particularly for patients achieving A1C levels ≤7.0%.^{11,12} Two studies, one in type 1 (Diabetes Control and Complications Trial [DCCT]) and one in type 2 diabetes patients (U.K. Prospective Diabetes Study [UKPDS]), compared conventional and intensive diabetes treatment regimens. In the DCCT, intensive insulin therapy resulted in a reduction in A1C of about 2%, from slightly >9.0% to slightly >7.0%, as well as a 63% to 69% reduction in the risk for

FIGURE 2 Lowering A1C Reduces Complications in Type 1 and Type 2 Diabetes

A1C	DCCT 9.1% → 7.3%	Kumamoto 9.4% → 7.1%	UKPDS 7.9% → 7.0%
Retinopathy	↓ 63%	↓ 69%	↓ 17%-21%
Nephropathy	↓ 54%	↓ 70%	↓ 24%-33%
Neuropathy	↓ 60%	Significantly improved	—
Macrovascular Disease	↓ 41%*	—	↓ 16%*

*Not statistically significant.

DCCT Research Group. *N Engl J Med.* 1993;329:977-86. Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-17. UKPDS Group. *Lancet.* 1998;352:837-53.

DCCT=Diabetes Control and Complications Trial; UKPDS=U.K. Prospective Diabetes Study.

FIGURE 3 UKPDS: β -Cell Function Over Time After Diagnosis

Data from UKPDS Group. *Diabetes.* 1995;44:1249-58.

UKPDS=U.K. Prospective Diabetes Study.

retinopathy. Nephropathy and neuropathy were similarly improved, with reported risk reductions of 54% and 60%, respectively. In the UKPDS, approximately 4,000 newly diagnosed T2DM patients received intensive therapy with a sulfonylurea or insulin. When necessary to achieve target glycemic control, metformin was added to the sulfonylurea, and insulin was added to the combination of oral agents. The conventional-therapy group was treated with diet alone; medications were added for hyperglycemic symptoms or for fasting blood glucose values >270 mg/dL. Over 10 years, the average A1C value was 7.0% in the intensive-therapy group and 7.9% in the conventional-therapy

group. The risk for any diabetes-related end point was 12% lower in the intensive-therapy group ($P=0.029$), and there was a 25% risk reduction in microvascular disease ($P=0.001$) (Figure 2).¹³

A growing body of evidence suggests that control of blood glucose also reduces the macrovascular complications of diabetes. The recent report from the researchers of the DCCT/Epidemiology of Diabetes Interventions and Complications study demonstrated that many years after the end of the DCCT, type 1 patients assigned to intensive treatment had a 42% lower risk for any cardiovascular outcome than patients in the conventional group and a 57% lower risk for nonfatal myocardial infarction, stroke, or death from cardiovascular disease, even though during most of the follow-up period there was little difference in the groups' A1C levels.¹⁴ There are 2 important messages from this study: improving glycemia will reduce the risk for macrovascular disease; and, while it is never too late to treat diabetes, the earlier treatment is begun, the greater the potential benefit because of an apparent "metabolic memory" of good or bad glucose control earlier in the course of the disease.

Moreover, a number of studies also highlight the importance of intensive control of the often-present hypertension and dyslipidemia among individuals with diabetes. In the STENO 2 trial, a treat-to-target, intensified intervention aimed at optimal control of multiple risk factors in patients with T2DM and microalbuminuria decreased cardiovascular and microvascular event risk by approximately 50%.¹⁵

Identifying Unmet Needs in Type 2 Diabetes Therapy: Revisiting Pathophysiology

The development of hyperglycemia in T2DM is the result of a number of core defects: insulin resistance, β -cell dysfunction, and increased hepatic glucose production. These defects have been shown to be present not only in frank diabetes but also in the prediabetic state, when glucose levels are lower than those required for the diagnosis of the disease.

Insulin Resistance

Insulin resistance is a state in which the cells of the body become resistant to the effects of insulin. That is, the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed to achieve appropriate blood glucose control. Obesity and physical inactivity contribute to insulin resistance, and it is now well recognized that insulin resistance is frequently associated specifically with deposition of intra-abdominal or visceral fat.¹⁶ If islet β cell function is normal, insulin output can be increased to overcome the diminished responsiveness of the insulin-sensitive tissues, thereby maintaining normal plasma glucose concentrations.¹⁷ It is this phenomenon that explains why not all individuals with insulin resistance and impaired glucose tolerance develop T2DM. When the β cell is unable to increase insulin output in response to changes in insulin sensitivity, hyperglycemia, prediabetes, and—ultimately—T2DM ensue.

β -Cell Dysfunction

All individuals with T2DM have at least a relative defect in the ability to secrete insulin from their β cells in addition to the often-present resistance to the action of insulin. The β -cell defect generally progresses over time. In the UKPDS, β -cell function had decreased to about 50% of normal at the time of diagnosis of diabetes and continued to decline over time despite therapy with diet, metformin, sulfonylureas, or insulin. (Figure 3).¹⁸

Qualitative abnormalities also exist in the insulin secretory responses in T2DM subjects. In particular, the first-phase insulin response seen 10 minutes after an intravenous (IV) glucose load in nondiabetic individuals is virtually absent in those with T2DM (Figure 4).¹⁹ This dysfunction occurs early in the disease history and contributes to the excessive postprandial glucose excursions characteristic of the disease. Postprandial peaks also contribute to wide glucose excursions and marked glycemic variability that typically occur in patients with T2DM, even when A1C is reasonably well controlled.²⁰

Loss of β -cell mass is also observed in association with loss of β -cell function. Autopsy studies have shown that β -cell mass is decreased by 50% to 60% in persons with T2DM, and the primary mechanism underlying this is increased β -cell death or apoptosis.²¹

The Role of Glucagon

The α cell and its secretion of glucagon are abnormal in T2DM. The role of glucagon is an often overlooked yet important element of T2DM pathophysiology. Secreted by pancreatic α cells, glucagon increases blood glucose via hepatic glycogenolysis or gluconeogenesis in the fasting state. After a carbohydrate meal, nondiabetic individuals suppress their glucagon secretion; this, in combination with a rapid insulin response, results in only modest rises in blood glucose. However, in those with T2DM, there is a diminished and delayed insulin response to a carbohydrate meal,²² and glucagon is not suppressed and indeed may be inappropriately elevated (Figure 5). As a result, hepatic glucose production is not decreased, and this contributes significantly to postprandial hyperglycemia.²³ Together, the impaired early insulin release and defective glucagon suppression result in elevated hepatic glucose production and increased plasma glucose concentrations. This phenomenon occurs early in the disease process, with defects in both α - and β -cell function apparent even in individuals with impaired glucose tolerance, the precursor to frank T2DM.

The Incretin Effect

When nondiabetic individuals are given an oral glucose load, their insulin levels are as much as 3 times greater than when the same subjects are given an IV glucose infusion to exactly match the plasma glucose levels seen with the oral load. This phenomenon, termed the “incretin effect,” is shown in Figure 6 and is defined as the difference in insulin response to oral versus intravenous glucose loads. In healthy individuals, up to 50% of postprandial insulin secretion is a result of the incretin effect.²⁴ In patients with

FIGURE 4 Loss of the Acute Insulin Response in Type 2 Diabetes

Ward WK et al. *Diabetes Care*. 1984;7:491-502.
Copyright© 1984, The American Diabetes Association.
IRI=immunoreactive insulin.

FIGURE 5 Glucagon Release in Normal Versus Type 2 Diabetes

Adapted from Mitrakou A et al. *Diabetes*. 1990;39:1381-90.

FIGURE 6 Measurement of the Incretin Effect: OGTT and Matched IV Infusion

Nauck MA et al. *J Clin Endocrinol Metab*. 1986;63:492-98.
Copyright© 1986, The Endocrine Society.
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IV=intravenous; OGTT=oral glucose tolerance test.

FIGURE 7 Metabolic Defects in T2DM: Current Therapeutic Targets

TZDs = thiazolidinediones.

FIGURE 8 Weight Change in UKPDS

UKPDS Group. *Lancet*. 1998;352:837-53. Copyright© 1998, Elsevier.
UKPDS = U.K. Prospective Diabetes Study.

T2DM, the incretin effect is diminished or absent.

Two gastrointestinal peptides have been identified as incretins: glucose-dependent insulintropic peptide (GIP) and GLP-1. Secretion of both incretins appears to be impaired in T2DM. GLP-1 has been the best studied of the incretins and is a more attractive therapeutic target as there appears to be resistance to GIP in T2DM. GLP-1 enhances insulin secretion in a glucose-dependent manner and has potential long-term effects that may preserve β -cell function and mass.²⁵ GLP-1 actions will be discussed in more detail later in this paper.

The understanding of incretins' role in glucose homeostasis has resulted in the focus on new targets for treatment and may offer promise for addressing some of the components of T2DM pathophysiology not addressed with traditional therapies.

Conventional Treatments

Several conventional therapies are currently recommended to treat

diabetes. Medical nutrition therapy and appropriately prescribed physical activity are the cornerstones of T2DM management but, as presently implemented and adhered to, are usually not sufficient to achieve glycemic targets.

There are also numerous pharmacologic agents that address the multiple pathophysiologic abnormalities in T2DM patients (Figure 7). Sulfonylureas and the nonsulfonylurea secretagogues, repaglinide and nateglinide, enhance endogenous production of insulin. Metformin lowers blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Thiazolidinediones address insulin resistance by enhancing glucose uptake by muscle and adipose tissue. The α -glucosidase inhibitors block the intestinal breakdown of complex carbohydrates into simple sugars and thereby delay and decrease postprandial hyperglycemia. Exogenous insulin is required in many T2DM patients when endogenous β -cell dysfunction progresses to the point that oral secretagogues and/or sensitizers are no longer able to achieve adequate glycemic control.

Achievement of Goals

Despite the extensive armamentarium of lifestyle measures and pharmacologic therapies to treat hyperglycemia in T2DM patients, most people with diabetes do not achieve recommended treatment goals. In data recently reported from the National Health and Nutrition Examination Survey (1988-1994 and 1999-2002) and the Behavioral Risk Factor Surveillance System (1995 and 2002) by Saaddine et al.,¹ there was limited improvement between the 2 periods of observation; the authors found that for the most recent period, only one third of patients had achieved an LDL-C of <100 mg/dL, less than half of patients had a systolic blood pressure of <130 mmHg, and only 42% had an A1C of <7%.

The *State of Diabetes in America* report released by the American Association of Clinical Endocrinologists (AACE) in 2005 demonstrated that 2 out of 3 individuals with T2DM did not achieve the A1C goals recommended by the ACE. The report, which analyzed a laboratory database of more than 157,000 people in 39 states during 2003 and 2004, found that 67% of patients had A1C levels higher than the ACE goal of $\leq 6.5\%$. In no state did more than half of the T2DM patients achieve this A1C goal.²⁶

Glycemic goals are not met for a number of reasons, including the failure of clinicians to adopt a structured treat-to-target approach, a lack of optimal health care delivery systems for people with chronic diseases like diabetes, and suboptimal patient adherence to lifestyle and pharmacologic treatments.

Even if short-term goals are met, glycemic control with most conventional therapies tends to deteriorate over time. In the UKPDS, fewer than half of subjects in all 5 treatment strategies evaluated—conventional, chlorpropamide, glyburide, insulin, and metformin—had A1C levels of <7% after 3 years, and after 9 years fewer than 25% were at this goal.²⁷ The loss of glycemic control is largely related to the progressive decline in β -cell insulin secretory function.¹⁸ Further, as noted above, even when A1C is

reasonably well controlled, postprandial glucose excursions often remain excessive with conventional therapies.²⁰

Most traditional therapies are associated with weight gain (Figure 8). In the UKPDS, weight gain was significantly higher (mean 2.9 kg) in the intensive pharmacologically treated group than in the conventional diet policy group ($P < 0.001$), and patients assigned insulin had a greater gain in weight (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg).¹³ Metformin and α -glucosidase inhibitors tend not to be associated with weight gain, and metformin may even be associated with weight loss in a significant number of people.²⁸

Insulin and insulin secretagogues are associated with significant risk for hypoglycemia. In the UKPDS, patients in the intensive group treated with insulin or sulfonylureas had more hypoglycemic episodes than those in the conventional group (both $P < 0.0001$).¹³

Adverse effects seen with many conventional therapies, such as the gastrointestinal side effects with metformin and the α -glucosidase inhibitors, edema and weight gain with thiazolidinediones, or hypoglycemia and/or increased weight with insulin or insulin secretagogues, may pose challenges for patient adherence and ultimately for the effective management of T2DM.

While present therapies should achieve far better results when they are used earlier and in combination, newer medications may help more patients achieve goals by addressing some of the limitations described above, including improving β -cell dysfunction and better regulating α -cell secretion of glucagon. In particular, incretin-related medications, including one that has recently been approved and several that are in late-stage development, show promise for exerting novel actions to target the unmet needs in T2DM management.

GLP-1 Therapeutic Potential Overview

GLP-1 has a number of antihyperglycemic actions, including increasing endogenous insulin secretion and decreasing glucagon secretion (both in a glucose-dependent manner); slowing accelerated gastric emptying often seen in T2DM subjects; and increasing satiety and decreasing food intake.²⁸ Studies have confirmed that GLP-1 infusions in individuals with T2DM can restore early insulin release and improve fasting and especially postprandial blood glucose levels.^{29,31}

The results of continuous GLP-1 infusion in T2DM patients are shown in Figure 9. GLP-1 infusion for 19 hours was associated with marked improvement in fasting and postprandial glycemia compared with placebo.³⁰ Zander et al. reported the results of a 6-week subcutaneous infusion of GLP-1 in 20 T2DM subjects.³² At the conclusion of the study, GLP-1 was associated with a reduction in A1C of 1.5% and in weight of 1.2 kg compared to placebo.

Chronically, GLP-1 may play an important role in the maintenance of β -cell mass. In animal and in vitro studies using human islets, β -cell mass increased, and the rate of programmed cell death, or apoptosis, decreased with the introduction of GLP-1.^{33,34}

FIGURE 9 GLP-1 Infusion Normalizes Blood Glucose in Patients With Diabetes

GLP = glucagon-like peptide.

Rachman J et al. *Diabetologia*. 1997;40:205-211.

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FIGURE 10 GLP-1 Release and Inactivation

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide.

Further studies will be required to investigate whether GLP-1-related therapy in humans will be able to decrease the progressive decline in β -cell mass and function characteristic of T2DM.

Clinical Data on Incretin-Based Therapies

Despite reported benefits of GLP-1 infusion in T2DM patients, clinical application is limited because of rapid degradation of GLP-1 by the enzyme DPP-4, which breaks down GLP-1 within minutes of the peptide's appearance in the circulation (Figure 10).

TABLE 2 Incretin Agents for Type 2 Diabetes Mellitus

Incretin Mimetics: GLP-1 Agonists/Analogues

Exenatide – FDA-approved (agonist)
Liraglutide – phase 3 trials (analogue)

Incretin Enhancers: DPP-4 Inhibitors

Vildagliptin – awaiting FDA approval decision
Sitagliptin – awaiting FDA approval decision
Saxagliptin – phase 3 trials

DPP=dipeptidyl peptidase; FDA=U.S. Food and Drug Administration;
GLP=glucagon-like peptide.

Continuous subcutaneous infusion of GLP-1, an impractical approach, would be required for the clinical use of native GLP-1. Alternative approaches to developing agents that would enhance GLP-1 receptor activation include GLP-1 analogues and receptor agonists (incretin mimetics) that resist degradation and agents that inhibit DPP-4 to increase the levels of endogenous GLP-1 (Table 2).

Exenatide

At present, the only U.S. Food and Drug Administration (FDA)-approved, incretin-based treatment is exenatide, a synthetic analogue of exendin-4, which is found in the salivary gland of the Gila monster. An effective GLP-1 agonist, it resists degradation by DPP-4 and has an extended half-life. It is administered subcutaneously twice a day (BID) at any time within the 60-minute periods before the morning and evening meals. Exenatide exhibits most of the antihyperglycemic actions of GLP-1, and a study by Fehse et al. demonstrated that loss of first-phase insulin secretion in T2DM patients may be restored by treatment with exenatide.³⁵

Three pivotal clinical trials led to the FDA's approval of exenatide. Exenatide 5 mcg or 10 mcg BID was compared with placebo in T2DM patients who had not achieved adequate glycemic control despite therapy with metformin and/or a sulfonylurea.³⁶⁻³⁸ From a baseline A1C of 8.2% to 8.6%, exenatide produced significant and dose-dependent declines in A1C levels in all 3 studies. Exenatide at 5 mcg BID resulted in A1C levels that were 0.48% to 0.78% lower than the A1C levels of those given placebo, while at 10 mcg BID, the A1C levels were 0.86% to 0.98% (Figure 11) lower than the A1C levels of those given placebo.

Exenatide was also associated with weight loss in all 3 studies. The 5 mcg BID dose was associated with a weight loss of 0.3 kg to 1.3 kg, while the 10 mcg BID dose achieved reductions in weight of 0.7 kg to 2.5 kg compared with placebo at the end of the 30-week trial.

The incidence of hypoglycemia associated with the addition of either dose of exenatide to metformin monotherapy was about 5% and similar to that seen with the addition of placebo. This is the anticipated outcome for an agent that enhances insulin secretion in a glucose-dependent manner. However, the incidence of hypoglycemia rose to 36% when exenatide doses of 10 mcg BID were added to sulfonylurea treatment (Figure 12).

The most frequently observed adverse events with exenatide therapy are gastrointestinal, including nausea and vomiting. Though these effects tend to subside over time, about 40% of subjects report usually mild-to-moderate nausea, and 13% experience vomiting. However, only in about 3% of individuals were these symptoms severe enough to cause withdrawal from the trial. Other potential considerations with the use of exenatide are the inconvenience of twice-daily injections, the requirement for refrigeration between injections, and the cost.

Liraglutide

Several incretin-related therapies are in development. Currently in

FIGURE 11 Exenatide + Oral Agents

* $P < 0.01$ versus placebo; baseline A1Cs $8.6\% \pm 1.2\%$ [$\pm$ SD]; $8.2\% \pm 1.1\%$. Buse JB et al. *Diabetes Care*. 2004;27:2628-35. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. Kendall DM et al. *Diabetes Care*. 2005;28:1083-91. A1C=glycosylated hemoglobin; Met=metformin; SU=sulfonylurea.

FIGURE 12 Exenatide + Oral Agents

Buse JB et al. *Diabetes Care*. 2004;27:2628-35. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. Kendall DM et al. *Diabetes Care*. 2005;28:1083-91. ITT=intent to treat; Met=metformin; SU=sulfonylurea.

phase 3 trials, liraglutide (NN2211) is a long-acting, acylated GLP-1 analogue that is bound to albumin, resulting in a half-life of approximately 12 hours. Liraglutide, which has 97% homology with GLP-1, is administered by once-daily subcutaneous injections.

Its effects were seen in a 12-week trial comparing liraglutide with glimepiride in T2DM patients with a mean baseline A1C of 7.6%. Both therapies produced a reduction in A1C of about 0.75%, compared with placebo, but liraglutide was associated with only a negligible risk of hypoglycemia.³⁹ The addition of liraglutide or glimepiride to the regimen of T2DM patients taking metformin resulted in a greater but not statistically significant difference in A1C reduction with liraglutide. With the addition to metformin, liraglutide treatment was associated with a 2.5% decrease in body weight compared with a 0.9% increase with metformin plus glimepiride.⁴⁰ In this early study, gastrointestinal side effects were reported frequently but were rated acceptable and rarely interfered with continuation of liraglutide treatment. Liraglutide is currently in phase 3 clinical trials.

DPP-4 Inhibitors

The use of DPP-4 inhibitors to retard the degradation of endogenous GLP-1 is another possible avenue of incretin therapy. Reducing incretin catabolism can decrease plasma clearance and increase the elimination half-life of endogenous GLP-1.⁴¹⁻⁴³ Several DPP-4 inhibitors are in development, including saxagliptin, sitagliptin, and vildagliptin; more data have been reported with vildagliptin. This investigational, orally administered agent is a competitive and reversible inhibitor of DPP-4 and can be given once or twice daily.⁴⁴ DPP-4 inhibition by vildagliptin has been shown to result in 2- to 3-fold increases of endogenous GLP-1 plasma levels.^{45,46}

Vildagliptin

Therapy with vildagliptin has been shown to significantly reduce fasting and postprandial glucose levels and improve glycemia in T2DM patients.^{44,47} One study demonstrated that vildagliptin combined with metformin may prevent deterioration of glycemic control in T2DM patients for as long as 1 year.⁴⁸ In this study, placebo or vildagliptin 50 mg/day was added to metformin for an initial 12-week treatment period (n = 107); A1C fell by a mean 0.6% in the vildagliptin group but was unaltered in the placebo group. In a 40-week, blinded extension of this study (1 year total), A1C remained stable in the vildagliptin-metformin group (n = 42) and increased in those given placebo-metformin (n = 29); the mean 1-year between-group difference in A1C was -1.1% (Figure 13).⁴⁸ Of note, vildagliptin was weight-neutral, with no evidence of weight gain despite the improvement in glycemic control. These data are presented in Figure 13, which shows a significant difference favoring the addition of vildagliptin compared with placebo.

Meal-related insulin secretion based on C-peptide data and

FIGURE 13 Vildagliptin + Metformin

Average baseline A1C = 7.7% ± 0.1%.

Adapted from Ahrén B et al. *Diabetes Care*. 2004; 27(12):2874-80.

A1C = glycosylated hemoglobin; MET = metformin; PBO = placebo; ITT = intent to treat.

FIGURE 14 Vildagliptin (Neonatal Rat Model)

Adapted from Duttaroy A et al. *Diabetes* 2005;54(suppl 1):A141. Abstract 572-P.

insulin sensitivity assessed via oral glucose insulin sensitivity were examined in patients completing the above 1-year study who participated in all meal studies (n = 57). Results suggested that vildagliptin combined with metformin improved β -cell function and postmeal insulin sensitivity.⁴⁹

In animal studies (neonatal rats), a significant reduction in β -cell apoptosis was associated with vildagliptin.⁵⁰ After prolonged exposure, an increase in β -cell mass was observed, supporting neogenesis or regeneration (Figure 14). Long-term clinical studies need to be conducted to further substantiate these findings by demonstrating sustained near-normoglycemia without evidence of disease progression or β -cell loss.

Vildagliptin was well tolerated in clinical trials, with the

incidence of nausea or vomiting not different from placebo and a low incidence of hypoglycemia symptoms.

Sitagliptin

Sitagliptin is also a selective inhibitor of DPP-4, with a pharmacokinetic profile supporting once-daily dosing.⁵¹ With 100 mg oral doses, $\geq 80\%$ inhibition of DPP-4 is seen for as long as 24 hours; at least 2-fold rises in GLP-1 plasma levels are achieved with sitagliptin compared with placebo.⁵¹

In a 12-week, randomized study involving 552 T2DM patients, significant reductions in A1C compared with baseline were seen with sitagliptin 25-100 mg once daily or 50 mg BID; A1C decreases were greatest in the 100 mg daily group. As with vildagliptin and other antihyperglycemic agents, differences from placebo in A1C reductions achieved by sitagliptin were greater in patients with higher baseline A1C values; these differences were -0.3%, -0.6%, and -1.1% in patients with baseline A1C values of <7%, 7% to 8.5%, and 8.5% to 10%, respectively. Fasting plasma glucose fell in dose-related fashion with sitagliptin but rose in the placebo group. Sitagliptin did not affect body weight. Hypoglycemia was rare, occurring in 1 patient in each sitagliptin dose group.⁵² Sitagliptin has also been submitted and is under review by the FDA.

■ Incretins and Managed Care

As noted earlier, the cost of diabetes and its complications is estimated to be \$132 billion per year. Direct medical costs account for \$92 billion of the total, with most of that consumed by institutional care, such as hospitalization for complications. The cost of diabetes has been projected to rise to \$192 billion by 2010, which would significantly strain the U.S. health care system even further.⁹ Already, the annual per capita health care costs for patients with diabetes are 4 times higher than for those without diabetes—\$10,000 versus \$2,500.⁹ Despite these high costs, medications and supplies are only about 13% (or \$17.5 billion) of the total cost of diabetes.²

Intensive glycemic control for T2DM is cost effective. Several detailed cost-benefit analyses, including a Centers for Disease Control and Prevention (CDC) analysis of data from the UKPDS, have been performed. Using a hypothetical cohort of newly diagnosed individuals with diabetes, the CDC researchers followed each individual until death or age 95 years and calculated the incremental cost of intensive glycemic control to be \$41,384 per quality-adjusted life-year gained. The major differences between standard and intensive glycemic-control groups were the cost of complications and the cost of the medication intervention itself for the observation period. Intensive glycemic control saved about \$4,330 by decreasing complications, but the cost of the intervention was \$12,213, for a net cost of \$7,883 for the intervention.⁵³

The availability of newer antihyperglycemic agents may alter cost-effectiveness. Obviously, any additional benefits beyond

glycemic control may increase the probability that newer diabetes medications, such as incretin-based treatments, may be cost effective.

Which diabetes medications are considered favorably cost effective? A recent comparison of 3 therapeutic policies from the UKPDS sheds some additional light. The authors evaluated the economic efficiency of intensive blood glucose control with sulfonylurea or insulin; intensive blood glucose control with metformin for overweight patients; and tight blood pressure control of hypertensive patients. Metformin therapy was cost saving and increased quality-adjusted life expectancy.⁵⁴

Glycemic control improvement with metformin or sulfonylureas is similar and cannot explain the higher probability that metformin will be cost effective in the above analysis. Metformin reduced cardiovascular events and mortality in the UKPDS, which in turn reduced inpatient costs. This illustrates how nonglycemic benefits of antidiabetic agents can have important economic consequences. Thus, any economic analysis of anti-diabetic agents, including incretin-based therapies, should incorporate any potential nonglycemic advantages into the analysis.

There are no long-term clinical or cost-effectiveness data on incretin-based therapy, so the possible impact must be inferred from results of existing studies and knowledge of the comorbidities associated with diabetes. A conservative listing of the effects of incretin therapy on costs can reasonably include the potential durability of A1C reduction, weight maintenance or loss, and avoidance of hypoglycemia.

β -cell function continues to decline over time in those with T2DM and is often the reason multiple agents are needed to achieve target glycemic control. Although not yet demonstrated in humans, incretin-related therapies have the potential to preserve β -cell function and may result in more durable glycemic control.

Maintaining patients on fewer medications avoids the cost of each additional medication as well as associated implementation costs, such as monitoring, safety and efficacy visits, and laboratory work. In addition, incretin-based medications should be associated with a lower risk for hypoglycemia, a condition that can increase practitioner visits and phone calls; severe hypoglycemia can require emergency or hospital services.

The majority of people with T2DM are obese, and obesity-related costs can be significant. In a study of Kaiser Permanente enrollees, total annual health care costs were about \$2,100 for those with a BMI of 20 to 24.9 but were approximately 44% higher when a patient had a BMI of 35 or greater.⁵⁵ On the positive side, though not all data are congruent, intentional weight loss has shown to be associated with a 25% reduction in total mortality and a 28% reduction in diabetes-related mortality, even after controlling for initial BMI, socio-demographic factors, health status, and physical activity.⁵⁶ Weight loss of even 10 pounds was associated with these positive effects.

DPP-4 inhibitors are weight neutral, and trials with incretin mimetics have been associated with weight loss. Importantly, incretin mimetics were shown to cause weight loss even without

the added impetus of an educational intervention for diet or exercise. Weight-neutral medications for T2DM may have benefits as well,^{57,58} but only future studies will delineate the potential role of weight loss or weight neutrality with incretin-based therapy.

In conclusion, diabetes is a major cost to the health care system. Antihyperglycemic and nonglycemic effects of diabetes medications can affect their potential cost-effectiveness. Incretin-based therapies, with the potential for sustained improvement of the A1C level, avoidance of hypoglycemia, and weight neutrality or loss, may prove to be highly cost effective. Carefully performed pharmaco-economic analyses will be required to accurately delineate the cost-effectiveness of these medications.

Summary

Understanding the pathophysiology of the hyperglycemia of T2DM has allowed practitioners to better utilize presently available antihyperglycemic medications and has provided the pharmaceutical industry with information that can help develop new medications.

Most patients do not achieve glycemic targets with conventional antihyperglycemic therapy. This paper has reviewed some of the reasons that most patients do not achieve glycemic goals, including the limitations of many presently available medications. The potential of GLP-1-related therapies to address some of these limitations has also been reviewed. Incretin-related therapies will add to the pharmacologic armamentarium for people with T2DM and hopefully help more T2DM patients achieve therapeutic targets.

As the prevalence of T2DM continues to increase, the role of incretin-based therapies in the management of T2DM is likely to become increasingly important to all members of the diabetes treatment team, including the managed care pharmacist seeking to address the growing economic burden of this disease and its complications.

DISCLOSURES

This article is based on the proceedings of a symposium held on April 7, 2006, at the Academy of Managed Care Pharmacy's 18th Annual Meeting and Showcase in Seattle, Washington, which was supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation and sponsored by Medical Education Resources and Consensus Medical Communications. The authors received honoraria from Novartis Pharmaceuticals Corporation for participation in the symposium.

Lawrence Blonde, MD, discloses that he has been a consultant to, has received honoraria for presentations from, and/or has been an investigator or subinvestigator in clinical trials sponsored by, and/or has received research support from the following companies: Abbott Laboratories, Amylin Pharmaceuticals, Inc., AstraZeneca, Aventis Pharmaceuticals, Inc., Becton, Dickinson and Company, Bristol-Myers Squibb Company, Eli Lilly and Company, EMD Pharmaceuticals, Inc., GlaxoSmithKline, LifeScan, Inc., Merck & Co., Inc., Merck/Shering-Plough, Novo Nordisk A/S, Novartis Pharmaceuticals Corporation, Pfizer Inc, sanofi-aventis, Takeda Pharmaceuticals North America, and Wyeth.

Julio Rosenstock, MD, discloses that he has served on advisory boards and received consulting fees from Amylin Pharmaceuticals, Inc., Centocor, Inc., GlaxoSmithKline, Johnson & Johnson, MannKind Corporation, Novo Nordisk A/S, Pfizer Inc, sanofi-aventis, and Takeda Pharmaceuticals North America. He has received grant support from Amylin Pharmaceuticals, Inc., AstraZeneca,

Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, MannKind Corporation, Merck & Co., Novo Nordisk A/S, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sankyo, sanofi-aventis, and Takeda Pharmaceuticals North America.

Curtis Triplitt, PharmD, discloses that he has served as a consultant or speaker for Amylin Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, and sanofi-aventis.

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Continuing Education

What Are Incretins, and How Will They Influence the Management of Type 2 Diabetes?

In order to receive CE credit for this program, you must complete this form and the Posttest Answers/Program Evaluation form in addition to completing the posttest with a score of at least 70% (forms may be photocopied). Please fax or mail the completed forms to Medical Education Resources, 1500 W. Canal Ct., Littleton, CO 80123; fax: (303) 798-5731. Statements of credit will be mailed within 4 weeks of receipt of appropriate documentation of course completion.

- ☐ I verify that I have completed the program and posttest for "What Are Incretins, and How Will They Influence the Management of Type 2 Diabetes?"

Signature: _____ Date: _____

Please print your name as you would like it to appear on the CE certificate:

Last name: _____ First name: _____

Degree: _____ Specialty: _____

Organization _____

Address: _____

City: _____ State: _____ ZIP: _____

Daytime phone: _____ Fax number: _____

E-mail: _____

What Are Incretins, and How Will They Influence the Management of Type 2 Diabetes?

Medical Education Resources (MER) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. A total of 0.15 CEU (1.5 contact hours) will be awarded and a continuing education statement will be sent within 4 weeks to pharmacists for successful completion of this continuing education program, which is defined as receiving a minimum score of 70% on the posttest and completion of the Posttest Answers/Program Evaluation form. There is no fee for participation in this activity (if not submitted online—see note below). ACPE Universal Program No. 816-999-06-003-H01 (Release date: September 1, 2006; Expiration date: September 30, 2007)

Note: Continuing Education for this program is also available online at the AMCP.org Learning Center site at www.amcp.org (Learning Center/Obtain Online CE/CME). Upon successful completion of this program, you will automatically receive your CE statement. (There will be a \$10 processing fee for nonmembers; see payment instructions on site.)

Please indicate the correct answers on the Posttest Answers/Program Evaluation form.

- The cost of diabetes in 2002 in the United States has been estimated at
 - \$12 million.
 - \$132 billion.
 - \$82 billion.
 - \$25 million.
 - \$40 billion.
- The direct cost of diabetes medications constitutes the largest portion of the total cost of diabetes.
 - True
 - False
- Approximately what percentage of type 2 diabetes patients are meeting the recommended A1C target of <7%?
 - 90%
 - 10%
 - 40%
 - 60%
 - 75%
- Intensive control of blood glucose has been shown to
 - reduce the risk for retinopathy.
 - reduce the risk for nephropathy.
 - reduce the overall risk of microvascular complications.
 - reduce macrovascular complication.
 - All of the above
- All individuals with insulin resistance eventually progress to type 2 diabetes.
 - True
 - False
- The UKPDS found the following therapeutic approach(es) effective at preventing the decline of β -cell function over time:
 - Diet alone
 - Sulfonylureas
 - Metformin
 - Insulin
 - None of the above
- Diet/exercise, sulfonylureas, and metformin have not adequately addressed which pathophysiologic elements of diabetes?
 - Accelerated gastric emptying
 - Progressive β -cell dysfunction
 - α -cell regulation
 - Impaired incretin effect
 - All of the above
- The incretin effect is defined as
 - the difference in insulin response to oral and intravenous glucose loads.
 - the difference in blood sugar levels with different glucose loads.
 - the amount of insulin produced as a result of incretin release.
 - the process by which the pancreas produces insulin.
 - None of the above
- The incretin GLP-1 has been shown to promote the following in animal and human research:
 - Increased glucose-dependent insulin secretion
 - Increased satiety and decreased food intake
 - Decreased glucagon secretion
 - Delayed gastric emptying
 - All of the above
- The clinical utility of GLP-1 is limited due to
 - rapid degradation by GIP.
 - the relative resistance to GLP-1 found in type 2 diabetes.
 - rapid degradation by the DPP-4 enzyme.
 - significant gastrointestinal side effects.
 - None of the above
- Pivotal clinical trials of the GLP-1 receptor agonist exenatide demonstrated
 - reduction in A1C of 0.8% from baseline.
 - significant risk of hypoglycemia when used with metformin.
 - 10-12 kg weight loss over 1 year.
 - significant risk of severe site reactions from injections.
 - All of the above
- Phase 3 trial results suggest that which of the following statements are true regarding the use of DPP-4 inhibitors for the treatment of type 2 diabetes?
 - They improve A1C levels.
 - They can be administered orally.
 - They improve postprandial glucose levels.
 - They are well-tolerated, with low rates of side effects.
 - All of the above

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Participant's name: _____ Date: _____

Posttest Answers:

1. A B C D E	5. A B	9. A B C D E
2. A B	6. A B C D E	10. A B C D E
3. A B C D E	7. A B C D E	11. A B C D E
4. A B C D E	8. A B C D E	12. A B C D E

Medical Education Resources and Consensus Medical Communications respect and appreciate your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgment of participation for this activity.**

Please answer the following questions by circling the appropriate rating:

5 = Outstanding

4 = Good

3 = Satisfactory

2 = Fair

1 = Poor

Extent to Which Program Activities Met the Identified Objectives

Upon completion of this activity, participants should be better able to

• identify the percentage of T2DM patients who fail to reach therapeutic goals and the impact of this failure on cost, quality of life, and complication rates	5 4 3 2 1
• review the often-overlooked aspects of diabetes pathophysiology, including the role incretins play in the processes that contribute to glucose homeostasis	5 4 3 2 1
• review incretin-based therapeutic options, including GLP-1 analogues, GLP-1 agonists, and DPP-4 inhibitors, and understand their roles in current treatment regimens	5 4 3 2 1
• discuss the potential pharmacoeconomic implications of incretin-based therapies in the managed care setting	5 4 3 2 1

Overall Effectiveness of the Activity

The content presented

• was timely and will influence how I practice	5 4 3 2 1
• will assist me in improving patient care	5 4 3 2 1
• fulfilled my educational needs	5 4 3 2 1
• avoided commercial bias or influence	5 4 3 2 1

Impact of the Activity

- Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this conference:

- How committed are you to making these changes?

5 (Very committed) 4 3 2 1 (Not at all committed)

Future Activities

- Do you feel future activities on this subject matter are necessary and/or important to your practice?

☐ Yes ☐ No

- Please list any other topics that would be of interest to you for future educational activities:

- Please indicate which venue you prefer for obtaining continuing education. (circle selection)

Written monograph

Slides

Videos

Internet-based

Live sessions

Other:

NOTES

[illegible]

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