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Incretin Mimetics: Promising New Therapeutic Options in the Treatment of Type 2 Diabetes

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S13 Continuing Education*:

CE Submission Instructions and Posttest Worksheet

Target Audience

Managed care pharmacists, clinical pharmacists, pharmacy directors, and medical directors responsible for reviewing treatment strategies for people with diabetes

Learning Objectives

Upon completion of this program, participants will be better able to

1. understand the scope of the diabetes epidemic; its associated costs, morbidities and mortalities; and statistical forecasts for disease trends;
2. become familiar with the percentage of patients with diabetes who are not at glycemic goal and the ramifications of that therapeutic failure for managed care organizations;
3. review the advantages and disadvantages of current oral pharmaceutical regimens for patients with type 2 diabetes, including mechanisms of action, occurrence of adverse events, and expectations of effectiveness over time;
4. review the antidiabetic pipeline and the key clinical and economic issues inherent in introducing biologic and injectable therapies into the treatment regimen for patients with type 2 diabetes;
5. learn the role and potential of the new incretin mimetic class and its mechanism of action in addressing insulin resistance and beta-cell dysfunction, the core defects of type 2 diabetes; and
6. explore optimal approaches and potential management challenges to adoption of a new injectable therapy in the treatment of type 2 diabetes.

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Incretin Mimetics: Promising New Therapeutic Options in the Treatment of Type 2 Diabetes

JEREMY M. GLEESON, MD, FACP, FACE; DAVID M. BERENBEIM, MD, MBA, FACP; and ROBERT J. GILKIN, JR., RPh, MBA

ABSTRACT

OBJECTIVE: To review the current state of diabetes treatment from a clinical and management perspective and explore the role that new biologic pharmaceuticals may offer patients who fail to meet or maintain glycemic goals with existing treatment options.

SUMMARY: Key clinical areas involve the role that insulin resistance and beta-cell dysfunction/failure play in the progression of type 2 diabetes as well as current treatment modalities and how they address those core defects. Management issues include a discussion of the economics of the disease and the implications of the United Kingdom Prospective Diabetes Study (UKPDS)—that good glucose control reduces the occurrence of microvascular complications and improves quality of life for diabetic patients. While an intensive approach may be costly in the short term, statistics on the rising pandemic of the disease argue compellingly for early and aggressive treatment to delay fatal complications and improve the quality of life for persons suffering from type 2 diabetes.

Current pharmaceutical regimens are not successfully enabling patients with type 2 diabetes to reach glycemic goals. The ramifications of this failure have profound repercussions in the managed care organization environment. Fortunately, new treatment modalities are in various stages of development. These will be reviewed with a more in-depth exploration of the potential of incretin mimetics, a new biologic, injectable class of drugs for the treatment of type 2 diabetes. Emphasis will be given to exenatide, an incretin mimetic that demonstrates particular efficacy for patients not achieving glycemic goal with oral medications and are insulin naive.

Biologics are administered by injection or infusion and are generally costly. Apart from their cost, however, what is even more critical to managed care executives and decision makers is that these medications indicate a trend in pharmacotherapy, a groundswell of new medications. In addition, few practitioners and even fewer health care executives understand molecular medicine. The key message is that making formulary decisions about these pharmaceuticals will become more pressing every year.

CONCLUSION: Managed care executives will be faced with the significant challenge of investing their limited resources in the most clinically and fiscally responsible manner within a milieu of ever increasing pharmacologic options that could significantly strain budgets and result in less than optimal patient outcomes.

KEYWORDS: Diabetes, Oral antidiabetics, Incretin mimetics, GLP-1, Managed care

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In 2002, the prevalence of diabetes—both types 1 and 2—was 18.2 million individuals, or 6.3% of the entire U.S. population. Diabetes, especially type 2, which affects about 95% of those who have the disease, is a national epidemic that is exacting an enormous toll in terms of quality of life, productivity, and cost. For example, diabetes was the fifth-leading cause of death by disease in this country and the causative factor in excessive morbidity such as cardiovascular disease (CVD), blindness, kidney failure, and lower extremity limb amputation. People with diabetes are twice as likely to have CVD as those without, and CVD remains the leading cause of death among diabetic patients.¹

Statistical forecasts for the disease are alarming. The prevalence of diabetes is expected to double within the next 2 decades along with potentially significant increases in the incidence of CVD. High-risk groups include the elderly, African Americans, Hispanic Americans, Native Americans, relatives of people with diabetes, the overweight or obese, and children. The roles of a sedentary lifestyle and obesity appear to be clear contributors to the development of the disease among susceptible individuals.²⁻⁴ In fact, more than 80% of people with type 2 diabetes are overweight.⁵

■ The Cost of Type 2 Diabetes

Nationwide, the direct and indirect cost burden of diabetes in 2002 was estimated at \$132 billion. Measurable direct medical costs include general diabetes care, treatment of diabetic complications, hospitalization, nursing home care, and office visits. Indirect costs include lost workdays and reduced productivity, costs associated with restricted activity, permanent disability, and mortality. Per-capita medical expenses were \$13,243 for individuals with diabetes compared with \$2,560 for those without the disease.¹

Because hospitalization for treatment of diabetes and its complications represents nearly 44% of direct medical expenses, it is economically prudent for health care administrators, executives, and policy makers to be aware of best practices that will yield optimal glycemic control for patients with type 2 diabetes. As demonstrated in the United Kingdom Prospective Diabetes Study 41 (UKPDS), intensive blood glucose control among patients with type 2 diabetes increased treatment costs but also reduced the occurrence of complications and largely offset the cost of treating both microvascular and macrovascular complications. Delaying or preventing the morbidity associated with chronic hyperglycemia also measurably improved patients' quality of life, which was defined as "time free of complications."^{6,7}

Outside of the clinical trial setting, tight control of blood glucose is also associated with reduced medical costs. Analysis of medical charges among a cohort of 3,017 adult type 2 patients enrolled in a large health maintenance organization found that the higher the A1c (glycosylated hemoglobin [previously referred to in the literature as HbA1c]) measurement, the higher the associated

inpatient and outpatient costs. As A1c increased, medical costs also increased. For example, for every 1% increase in A1c from 6% to 10%, cumulative charges increased by 4%, 10%, 20%, and 30%, respectively.⁸

In another retrospective database analysis, researchers found that, from 1994 to mid-1998, patients with good glycemic control, defined as A1c <8%, had mean adjusted charges of \$970. These findings compared with patients with fair control (A1c 8% to 10%) and charges of \$1,380 versus patients with poor control (A1c >10%) with charges of \$3,040. Not surprisingly, among those members of the cohort with complications, differences in mean medical charges were greater. The researchers concluded that, in a typical managed care organization (MCO), better glycemic control contributes to short-term economic gain.⁹

Aggressive pharmaceutical treatment and tighter glycemic control are associated with overall cost benefits.^{7,8} When evaluating the economics of a variety of pharmaceutical therapies, it should be noted that pharmaceutical costs represent <10% of the total cost of diabetes therapy; the majority of costs are related to hospitalizations and treatment of complications.¹⁰ At the present time, MCOs are treating increasing numbers of patients with type 2 diabetes, and drug therapy costs for this group of patients continue to grow, leaving many managed care executives with the perception that drug costs for persons with diabetes require greater scrutiny. Researchers stress, however, that seemingly dramatic increases in drug expenditures must be measured against fewer diabetes-related complications and the higher cost of treating them, especially in inpatient environments.¹¹

■ Pathophysiology and the Natural History of the Disease

Type 2 diabetes is an endocrine/metabolic disease characterized by hyperglycemia. It develops when the liver and peripheral tissues, such as muscle, become resistant to insulin and when the beta cells of the pancreas produce insufficient insulin to overcome this insulin resistance (IR).¹²

Insulin Resistance

IR is part of a dangerous syndrome—known as the insulin resistance syndrome, syndrome X, or the metabolic syndrome—that occurs in about 25% of western populations or about 47 million people in the United States alone. This syndrome is a collection of cardiovascular risk factors including hypertriglyceridemia, hypertension, and obesity. Individuals with IR syndrome are at an increased risk for coronary artery disease (CAD), morbidity, and mortality. Immediate and aggressive treatment of the IR syndrome is essential to avoid diabetes, CAD, and stroke.¹³⁻¹⁵

The progression from normal glucose tolerance to impaired glucose tolerance to overt type 2 diabetes is a result of declining beta-cell function in the face of IR, which some researchers believe is the first stage of the disease continuum.¹⁶ Both declining beta-cell function and IR are core pathological defects in the development of frank type 2 diabetes.^{17,18}

FIGURE 1 Data From UKPDS 16

UKPDS = United Kingdom Prospective Diabetes Study.

TABLE 1 First- and Second-Phase Insulin Response

The exposure of beta cells to glucose results in a rapid (3 to 5 minute) increase in insulin secretion (first-phase insulin secretion) followed by a decrease in about 10 minutes to basal rates. If exposure to glucose is prolonged, a slower, second-phase insulin secretion occurs. Second-phase insulin secretion occurs after 10 to 20 minutes. Among diabetic subjects, chronic exposure to glucose results in a reduction in insulin secretion due to the desensitization and/or exhaustion of the beta cells to glucose.¹⁹

Indication of Beta-Cell Dysfunction

Loss of first-phase insulin response after ingestion of glucose (as a regular meal or in the medical setting as a glucose challenge) is an early sign of beta-cell dysfunction. Later, and in the natural progression of the disease, impaired second-phase insulin secretion occurs. Postprandial and fasting hyperglycemia are indicative of beta-cell dysfunction and failure. Further, sustained hyperglycemia and type 2 diabetes will result in many individuals with IR and beta-cell dysfunction.²⁰

The landmark UKPDS demonstrated that type 2 diabetes is a progressive disease with deteriorating glucose control. This most likely stems from declining beta-cell function.¹⁸ Despite the mode of therapy—diet and exercise, sulfonylureas, or metformin—glucose control inevitably declines (see Figure 1 and Table 1).

The Natural Course of the Disease

Diabetes is typically diagnosed years to decades after the onset of IR and declining beta-cell function. This lag in diagnosis has serious consequences because both microvascular and macrovascular damage has often occurred prior to clinical identification of the disease.

The natural course of diabetes results in chronic hyperglycemia, as measured by increasing levels of A1c over time. If left untreated, hyperglycemia leads to serious microvascular and macrovascular complications involving many major organ systems.²¹ Frequently, by the time hyperglycemia is identified, disruption of the normal relationship between beta-cell function and insulin sensitivity is well established.

The most common macrovascular complications associated with type 2 diabetes are myocardial infarction and stroke. In fact, more than 65% of people with diabetes die from heart disease or stroke. Coronary artery disease is the most common cause of death among individuals with diabetes.²² Microvascular complications include peripheral neuropathy, nephropathy, and retinopathy. The sequelae of these 3 complications are lower extremity amputation, kidney failure, and blindness. All 3 complications are common among patients with diabetes, especially those who do not maintain glycemic control.²³

The UKPDS and numerous subsequent studies demonstrated that delay or even prevention of the microvascular and macrovascular complications of type 2 diabetes may be achieved with tight glycemic control. Tight glucose control was defined as a fasting plasma glucose <6 mmol/L (108 mg/dL).²⁴ Therefore, a logical goal of diabetes treatment is the preservation of beta-cell function and the prevention of diabetic complications. Specifically, this means maintaining glycemic measures within acceptable ranges.

The UKPDS 35 documented that any reduction in A1c reduces complications, i.e., each 1% reduction in A1c is associated with a 21% risk reduction for any diabetic microvascular or macrovascular end point. Also documented in this study was that the lowest risk for development of diabetic complications was observed in those with A1c <6.0%.²⁵ The American Diabetes Association (ADA) stresses that any A1c above 7% is potentially harmful, and even lower values may be beneficial.²³ In addition to these documented clinical benefits, published studies strongly indicate that aggressive use of antidiabetic agents is associated with an overall cost benefit as well.²⁶

Current Treatment Modalities

A Review of the Oral Options

An initial therapeutic approach of diet and exercise is followed by a progression of monotherapy with oral antidiabetics (OADs), combination OADs, or OADs in conjunction with insulin to control blood glucose levels.¹⁷

The 5 classes of oral medications currently available to treat diabetes— α -glucosidase inhibitors, biguanides, meglitinides, sulfonylureas, and thiazolidinediones—work through differing mechanisms of action to increase peripheral glucose uptake, inhibit glucose release by the liver, or stimulate insulin output:²⁷⁻²⁹

- **α -glucosidase inhibitors** delay the absorption of polysaccharides and also act to attenuate postprandial glucose excursions; mean reduction in A1c=0.5% to 1.0%
- **biguanides**, including metformin, reduce hepatic glucose out-

put; mean reduction in A1c=1.0% to 1.5%

- **meglitinides** are rapid-acting insulin secretagogues that target postprandial glucose excursions; mean reduction in A1c=0.5% to 1.0%
- **sulfonylureas** are insulin secretagogues; mean reduction in A1c=1.0% to 1.5%
- **thiazolidinediones** are insulin sensitizers that improve glucose uptake in adipose tissues and skeletal muscles; mean reduction in A1c=1.0% to 1.5%¹⁰

Drawbacks to the Oral Therapies

The current oral treatment modalities outlined above, while generally effective in the short-term, are associated with a number of drawbacks and adverse events including weight gain, hypoglycemia, gastrointestinal disturbances, edema, potential liver dysfunction, loss of effectiveness over time leading to the eventual need for combination or fixed-dose combination therapy and exogenous insulin, limited ability to protect beta cells, and, with some of the newer drugs, high cost.³⁰

While oral therapies are currently the mainstay of treatment for patients with type 2 diabetes, their inherent disadvantages and eventual inefficiency, as demonstrated by the UKPDS and other researchers, point to the critical need for more effective therapeutic options. Individuals who fail diet and exercise as initial therapy are prescribed oral monotherapy. After 6 years, however, nearly 50% of patients require additional oral therapies to maintain glycemic control. Among UKPDS subjects, nearly 50% of subjects at 3 years were unable to maintain their target levels of A1C <7% by utilizing a monotherapy approach.³¹

In the next section, we will outline how limitations of current oral therapies affect MCOs and their patients with type 2 diabetes. This discussion will be followed by an exploration of incretin mimetics, first-in-class injectable, antidiabetic agents that have a novel mechanism of action and indicate a new and potentially promising approach to the pharmaceutical management of type 2 diabetes.

The Need for More Effective Therapies

Diabetes diagnosis and treatment to goal must be a priority for health care providers, payers, policy makers, educators, and employers. The ADA recommends an A1c level of <7%, and the American College of Endocrinology (ACE) endorses lowering the A1c goal to $\leq 6.5\%$.³² Table 2 illustrates widely published achieved versus desired A1c goals in large populations of diabetic individuals.

Despite numerous published studies and widely disseminated, scientifically robust clinical practice guidelines, standards of care for most persons with diabetes in the United States still do not meet national recommendations.^{35,36} In fact, 63% of patients with type 2 diabetes on drug therapy are not at A1c goal of <7.0%, and 37% have an A1c >8%.³⁷

The reasons for this failure of therapy are varied and complex.

Diabetes is a multisystem disorder that requires multidisciplinary team care. Effective management of the disease must include patient and provider education, lifestyle modification, and behavior modification to achieve glycemic goals.⁶ An informed, involved patient is key to the success of any diabetes treatment program. Since most patients with diabetes eventually will require more than one oral antidiabetic agent to control glycemic levels, patient preference is also a valid consideration when choosing a pharmacological regimen.³⁸

In addition to the best choice of a therapeutic regimen, the timing of initiation of therapy is also critical. Numerous published studies point to the rationale for early, aggressive treatment to delay or prevent diabetic complications rather than treating patients in a reactive manner.³⁹⁻⁴¹

Achieving and maintaining glycemic goals, reducing weight, delaying and/or preventing the complications of type 2 diabetes, improving the quality of life for patients, and controlling costs associated with the management of diabetic complications comprise the rationale for better therapeutic options for the treatment of type 2 patients. The evidence suggests that these goals are not adequately being achieved by utilizing current treatment modalities. Therefore, to achieve the currently elusive universal glycemic control for their type 2 patients, health care providers and administrators can look to the pipeline for antidiabetic agents that might hold more promising treatment options (Table 3).

While the focus of this supplement is on the incretin mimetic exenatide, it is appropriate to provide an overview of the other antidiabetic drugs in late stages of development; where applicable, brand and generic drug names are given.

Amylinomimetic Drug: Pramlintide Acetate (Symlin)

Pramlintide acetate is a synthetic version of the human hormone amylin. It is the first member of a new class of therapeutic medications known as amylinomimetic agents, or amylin receptor agonists. Amylinomimetic agents mimic the actions of the hormone amylin and demonstrate efficacy in regulating blood glucose levels. In persons without diabetes, the naturally occurring hormone, amylin, works in conjunction with insulin and glucagon to maintain euglycemia.

More than 5,000 patients have completed 6 Phase 3 clinical trials of pramlintide in addition to long-term, open-label safety and Phase 3 extension trials. In all of these, intervention subjects demonstrated reductions in A1c of 0.3% to 0.6%. Pramlintide-treated patients also experienced weight loss >3 pounds, while those treated with either insulin only or placebo gained weight.

In persons with insulin-requiring type 2 diabetes, pramlintide prevented the abnormal rise in glucagon after meals, slowed the rate of gastric emptying, and reduced postprandial glucose excursions. Pramlintide is indicated for persons with type 1 diabetes as an adjunctive therapy for those currently using mealtime insulin or for type 2 diabetes patients as an adjunct to mealtime insulin with or without concurrent sulfonylurea and/or metformin.⁴²

TABLE 2 Achieved Versus Desired A1c Levels

Recommended A1c goals	
American Diabetes Association ²⁶	<7%
American College of Endocrinology ³²	<6.5%
A1c achieved in clinical trials	
UKPDS intensively treated patients (median over 10 years) ³³	7.0%
UKPDS conventionally treated patients (median over 10 years) ³³	7.9%
A1c achieved in clinical practice	
NHANES III (ages 20-54) ³⁴	7.8%
NHANES III (ages 55-64) ³⁴	7.6%

A1c = glycosylated hemoglobin; NHANES III = Third National Health and Nutrition Examination Survey; UKPDS = United Kingdom Prospective Diabetes Study.

TABLE 3 The Pipeline of Antidiabetic Drugs

Drug Class	Drug Name	MOA	Phase	Comments
Amylinomimetic	Pramlintide acetate* (Symlin)	Amylin agonist	FDA approved March 2005*	Injectable
Incretin mimetics	Exenatide* (Byetta)	A GLP-1 agonist	FDA approved April 2005*	Injectable
	LAF237 MK-0431 (Sitagliptin)	DPP-IV inhibitor DPP-IV inhibitor	Phase 3 Phase 3	Oral medication Oral medication
PPAR agonists	Tesaglitazar (Galida)	Dual-acting PPAR agonist	Phase 3; but regulatory filing delayed until 2007	Potential to treat both type 2 diabetes and associated lipid abnormalities
	Muraglitazar (Pargluva)	Dual-acting PPAR agonist	NDA filed	Oral medication

* At the time of the October 14, 2004, Academy of Managed Care Pharmacy's 2004 Educational Conference when this information was presented, both pramlintide and exenatide were still in Phase 3 clinical trials.

DPP-IV = dipeptidyl peptidase IV; FDA = U.S. Food and Drug Administration; GLP = glucagon-like-peptide; MOA = mechanism of action; NDA = New Drug Application; PPAR = peroxisome proliferator-activated receptor agonist.

Incretin Mimetic Drugs

LAF237

This agent is the first in a new class of dipeptidyl peptidase IV (DPP-IV) inhibitors. LAF237 works by blocking the action of DPP-IV, an enzyme that normally inactivates glucagon-like-peptide-1 (GLP-1). A full discussion of the action of GLP-1 and incretin mimetics follows this section.

Preliminary data suggest that LAF237 may improve glycemic control in patients with type 2 diabetes who also take metformin but are not adequately controlled on this medication alone. Phase 2 clinical trial summaries suggest that patients who were part of the

FIGURE 2 Insulin Secretion in Nondiabetic Individuals Versus Persons With Diabetes

metformin plus LAF237 treatment cohort sustained an A1c level that was, on average, 1.1% lower than the group receiving metformin plus placebo. Fasting and postprandial glucose levels were also reduced in the intervention group versus those on metformin alone. In addition, the metformin plus LAF237 group sustained lower A1c levels for 1 year. In contrast, researchers saw an increase in A1c in the metformin-only group during the same period.⁴³

According to trial summaries, LAF237 is considered well tolerated, with 76.2% of subjects completing the 52-week Phase 2 trials. Sixty-nine percent of intervention subjects reported an adverse event, which was primarily hypoglycemia but not considered serious.⁴³

Sitagliptin

Sitagliptin is also a DPP-IV inhibitor but is not as far along the development curve as is LAF237 and has fewer released data, especially regarding the outcomes of Phase 2 trials. Press releases indicate that sitagliptin effectively blunts postprandial glucose excursions and plasma glucagon while increasing the amount of circulating GLP-1, plasma insulin, and plasma C-peptide, compared with placebo. Sitagliptin subjects were also being treated with thiazolidinediones (TZDs), diet, and exercise. Sitagliptin appears to have been well tolerated in clinical trials.⁴³

PPAR Agonist Drugs

Tesaglitazar

Tesaglitazar is a dual-acting oral peroxisome proliferator-activated receptor (PPAR) agonist. It is a member of a new class of drugs with potential for treating glucose and lipid abnormalities associated

with type 2 diabetes and the metabolic syndrome. Dual-acting PPAR agonists are a novel group of compounds that activate both PPAR-alpha and PPAR-gamma receptors and simultaneously reduce atherogenic triglycerides, raise cardioprotective high-density lipoprotein levels, and improve insulin resistance. These multiple mechanisms of action address many of the core abnormalities seen in people with metabolic syndrome and may help reverse the underlying disease process and its adverse clinical sequelae, which include CVD and diabetes.

Drugs that target only PPAR-gamma receptors, the TZDs, are insulin-sensitizers currently used in the treatment of type 2 diabetes. These agents reduce blood glucose levels but have a tendency to cause weight gain. Dual-acting PPAR agonists may be able to achieve therapeutic benefits without the weight gain associated with TZDs. Clinical studies suggest tesaglitazar is well tolerated. However, safety will be a critical issue with this drug because several promising candidates in the same class have demonstrated adverse toxicity profiles.⁴⁴

Muraglitazar

Muraglitazar is another dual-acting PPAR agonist with the potential to treat both blood glucose and lipid abnormalities in patients with type 2 diabetes. If the New Drug Application is approved by the U.S. Food and Drug Administration (FDA), muraglitazar will likely be the first in this novel class of drugs to be sold in the United States.⁴⁵

Clearly, there is a need for additional outcomes data and cost-effectiveness studies on all of the pipeline drugs. These studies must be widely disseminated in peer-reviewed journals before accurate and comprehensive decisions can be made regarding the merits and cost-effectiveness of any novel therapeutic approach.

The following section will first explore the mechanisms of action of GLP-1. It will then examine published study results for exenatide, a GLP-1 agonist and synthetic exenatide compound.

GLP-1: A Novel Antidiabetic Approach

Postprandially, gut hormones are released that stimulate insulin secretion; these are called incretin hormones. In humans, the most important incretin hormones are the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1). Persons with impaired glucose tolerance or type 2 diabetes have a deficient postprandial GLP-1 response that may contribute to the decreased incretin effect among this population.⁴⁶ Figure 2 illustrates the significant differences in postprandial insulin secretion between a group of healthy volunteers and a cohort of persons with type 2 diabetes.¹⁹

Glycemic control is achieved in part by GLP-1's ability to restore the first-phase insulin response and suppress glucagon.⁴⁷ Glucagon is a hormone that opposes the action of insulin in peripheral tissues, particularly the liver. Although meals generally suppress glucagon secretion, persons with diabetes frequently exhibit abnormal glucagon secretion, leading to failure to suppress

hepatic glucose production and the presence of fasting hyperglycemia.

Overall, GLP-1 exhibits the following antidiabetogenic properties:⁴⁸⁻⁵¹

- glucose-dependent stimulation of insulin secretion
- inhibition of glucagon secretion
- delayed gastric emptying
- increased satiety and reduced food intake
- improved insulin sensitivity
- increasing beta-cell mass (stimulation of new pancreatic islet cells and a slowing of beta-cell apoptosis)

In several small clinical trials, the effect of GLP-1 on appetite and satiety was investigated. Overall, in both normal weight and obese subjects, intravenous infusion of GLP-1 suppressed hunger, slowed gastric emptying, and enhanced satiety compared with placebo. Subjects receiving the GLP-1 infusion ate 12% to 27% less than subjects receiving placebo. Study authors conclude that GLP-1 may be beneficial in weight reduction, a critical goal for overweight or obese type 2 patients because weight loss has been demonstrated to improve insulin resistance and the glycemic profile.⁵²⁻⁵⁴

In a study to examine the effect of GLP-1 on appetite, plasma glucose, insulin, glucagon, postprandial lipidemia, blood pressure, heart rate, and basal metabolic rate, researchers infused study subjects with 2.4 pmol/kg/minute of GLP-1 or saline subcutaneously (SC) for 48 hours. Results indicated that both fasting and meal-related plasma glucose were lowered among patients in the intervention arm. Reduced appetite, absence of gastrointestinal side effects, and a slight reduction in blood pressure were also reported for intervention subjects. Triglycerides, free fatty acids, and basal metabolic rates were not effected.⁵⁵

Dose-dependency studies demonstrate that glucose normalization can be achieved with as little as 0.4 pmol GLP-1/kg/minute. In a study examining 3 different GLP-1 infusion rates, 0.4, 0.8, and 1.2 pmol/kg/minute versus a saline placebo, the lowest of the concentrations of GLP-1 was found to effectively lower blood glucose and slow gastric emptying, indicating that lower GLP-1 doses than previously utilized in clinical trials may be efficacious for glucose control in type 2 patients.⁵⁶

GLP-1 has the potential to preserve the beta-cell function, which could halt or delay the progressive deterioration of body systems normally seen in patients with type 2 diabetes.⁵⁷ Further promise regarding the effect of GLP-1 on beta cells was seen in animals where GLP-1 may actually increase beta-cell mass, size, and maintain beta-cell efficiency.^{58,59}

While the antidiabetogenic properties of GLP-1 are promising, the hormone in its natural form is rapidly degraded and is therefore not effective in the clinical treatment of type 2 diabetes. However, synthetic, long-acting GLP-1 receptor agonists are now emerging as potent agents for the treatment of type 2 diabetes. In the following section, the synthetic peptide, exenatide, will be examined in greater depth.

The Incretin Mimetic Exenatide

Exenatide is characterized in the literature as a biopharmaceutical, that is, any therapeutic agent that structurally mimics compounds found within the human body.⁶⁰ Exenatide is derived from the saliva of the Gila monster—a poisonous lizard native to the American Southwest—and has a novel mechanism of action with similarities to naturally occurring GLP-1. It is a first-in-class injectable antidiabetic agent that has a significant effect on glucose homeostasis, insulin sensitivity, beta-cell performance, and weight loss. Phase 3 clinical studies in excess of 6 months conducted among patients not adequately controlled with oral medications indicated that synthetic exenatide has demonstrated efficacy in improving glucose homeostasis.⁵¹

In a study to examine various aspects of exenatide as an antidiabetic agent, researchers recruited both nondiabetic and type 2 diabetic subjects. All subjects underwent a 5-hour hyperglycemic clamp (fasting plasma glucose level + 5.4 mmol/l [97 mg/dL], and exenatide infusion was added at 60 minutes after the start of the glucose clamp. With the addition of exenatide to the infusion, plasma insulin response was raised 4 to 5 times above that achieved during the first 60 minutes of the hyperglycemic clamp alone and remained elevated for several hours. After terminating the clamp and allowing the plasma glucose to return toward basal levels, all subjects ate a meal. Postprandial plasma glucose, insulin, and GLP-1 did not rise in any subject. Study authors attribute this to delayed gastric emptying associated with exenatide. They conclude that synthetic exenatide is a potent and long-lasting insulinotropic agent in patients with and without diabetes.⁶¹

The published literature also reports insulin-naïve, type 2 diabetes patients' changes in A1c, blood glucose measurements, beta-cell sensitivity to glucose, and peripheral tissue sensitivity to insulin before and after a 1-month treatment protocol with twice-daily, SC, self-injected exenatide. The greatest change in blood glucose measurements was seen in the bedtime levels that had been 15.5 mmol/l at baseline and dropped to 9.2 mmol/l (279 mg/dL and 166 mg/dL, respectively) at study's end. The A1c dropped from 9.1% at baseline to 8.3% at 30 days. Beta-cell sensitivity to glucose also improved. No significant adverse events were experienced by study subjects. The authors interpret their data to suggest that, even given a short duration of therapy, exenatide treatment can produce a significantly positive effect on glucose homeostasis.⁶²

Similar effects on postprandial glucose, postprandial glucagon, fasting plasma glucose, and insulin have been observed. Gastric emptying and reduced caloric intake have also been measured and noted, with study authors concluding that exenatide may be a potent treatment for type 2 diabetic patients, especially those who are obese.⁶³ Figure 3 demonstrates the effect of a single dose of SC exenatide administered 15 minutes prior to a standard liquid meal test on postprandial glucose concentrations (left panel) and on postprandial glucagon concentrations (right panel) in people with type 2 diabetes.⁶⁴

FIGURE 3 Exenatide and Postprandial Glucose

Effect of Exenatide on Postprandial Glucose and Glucagon in Type 2 Diabetes

n = 20
Mean ± SE

Data from Kolterman OG, et al. *J Clin Endocrinol Metab.* 2003;88:3082-89.

No study to date has reported a serious risk of hypoglycemia among study participants. Side effects, primarily nausea, are mild and transient.⁶⁵ The FDA-approved initial dose is 5 mcg twice daily anytime within 60 minutes prior to the morning and evening meal. Exenatide should not be administered after a meal. Based on the clinical response, the dose can be increased to 10 mcg twice daily after 1 month of therapy.⁶⁶

Exenatide is recommended for use with metformin and/or sulfonylurea. Fineman and colleagues conducted a study of 109 patients treated either with diet and a sulfonylurea and/or metformin who were not achieving optimal glucose control. Patients self-injected either exenatide (0.08 mcg/kg) or saline SC for 28 days. Glycemic control in the intervention group, as measured by reductions in serum fructosamine and A1c, was significantly improved compared with the placebo group. For example, reductions in A1c ranged from 0.7% to 1.1%. At study end, 15% of intervention subjects achieved an A1c of <7% while only 4% of placebo subjects achieved this goal. Beta-cell index, measured by the homeostasis model assessment, was 50% to 100% higher at study end compared with baseline for intervention subjects. Beta-cell index was unchanged among placebo patients. The authors conclude that exenatide is a promising new agent for the treatment of type 2 patients.⁶⁷

Phase 3 and Beyond

All 3 pivotal Phase 3 studies conducted by the manufacturer of exenatide met the primary glucose control end point, using reduction in A1c as the metric. Reductions in body weight were

also captured.

Results of one of the 3 studies were presented at the 64th Annual Scientific Session of the ADA in 2004.⁶⁸ In the abstract, the effects of exenatide added to the therapeutic regimen of patients not achieving glycemic targets at maximally effective doses of metformin (at least 1,500 mg/day) were evaluated. This was a randomized, triple-blind, placebo-controlled, 30-week trial. The 3 study cohorts (n = 336) were the placebo arm, patients injecting 5 mcg of exenatide, and 10 mcg of exenatide SC twice daily. All subjects continued on their metformin regimen throughout the 30-week period; 272 (81%) of the patients completed the study.

At week 30, mean reductions in A1c from baseline were -0.86% for the 10 mcg cohort, -0.46% for the 5 mcg cohort, and no change for the placebo group, $P < 0.01$. Overall, of the 3 groups with baseline A1c > 7%, 46%,

32%, and 13%, respectively, achieved A1c ≤ 7% at the study's end, $P < 0.01$. Fasting and postprandial glucose levels also decreased in both exenatide-treated cohorts.

Weight loss was observed in the intervention subjects, with the 10 mcg cohort losing an average of 2.8 kg and the 5 mcg cohort losing 1.6 kg; placebo-treated subjects lost 0.3 kg, $P < 0.05$. Additionally, beta-cell secretory function increased in both intervention groups.⁶⁸

When results were aggregated by the manufacturer from all patients completing the 3 pivotal Phase 3 studies, the average reduction in A1c was approximately 1% and occurred among those patients on the highest dose of exenatide (10 mcg twice daily). In addition, approximately 40% of these patients achieved A1c levels of ≤ 7%. On average, subjects in the Phase 3 clinical trials on 10 mcg of exenatide twice daily also demonstrated statistically significant reductions in body weight of approximately 2 kilograms.⁶⁶

The most common adverse event among subjects participating in clinical exenatide trials was mild-to-moderate transient nausea. The overall incidence of nausea was 31% and occurred most commonly during commencement of treatment. No hypoglycemia requiring the assistance of another person was seen in any subject.⁶⁶

As a result of these Phase 3 clinical studies, exenatide is approved for those patients who are not achieving glycemic control with a sulfonylurea and/or metformin regimen and are insulin naive. It is designed to be an adjunct to the above agents.

Lastly, a published review indicates that exenatide and GLP-1

appear to increase beta-cell mass by way of stimulation of beta-cell neogenesis, stimulation of beta-cell proliferation, and suppression of beta-cell apoptosis.⁶⁹ Additional studies are needed to support these provocative results.

■ Management Issues Associated With Biologics, Including Incretin Mimetics

Management issues are associated with the use of all biologics, including the incretin mimetics. These include

- growth of the entire market
- generally high cost with resultant shifting definitions of pharmacy versus medical benefits, increased patient cost sharing, and use of tiered formularies
- frequent need for injection and/or infusion
- distribution of injectables through specialty pharmacy companies

These important and unique aspects of biologics require awareness from health care executives and decision makers regarding optimal management strategies for such medications.

Growth of the Biologics Market and Inevitable Cost Increases

Literally dozens of biopharmaceutical agents are nearing approval for 156 late-stage indications in 36 disease categories. Diabetes, cardiovascular disease, obesity, osteoporosis, stroke, and allergies are the disease states where the largest numbers of potential patients may become eligible for treatment.⁶⁰

Given their potential for enhanced clinical outcomes, biologics should be accessible to appropriate patient populations. However, this decision inevitability presents a management challenge due to the fact that costs to payers will rise. For example, Medco—a pharmacy benefit management company with the nation's largest mail-order pharmacy business—predicts that spending on “specialty pharmaceuticals” will reach \$40 billion by the end of 2006, a growth rate double that of the national average increase in nonspecialty drug spending.⁷⁰

Shifting Definitions of Pharmacy Versus Medical Benefits

On a micro scale, researchers have speculated that the shift of biologic drug administration from inpatient to outpatient settings—or, as is the case with many of the diabetes pipeline drugs, in the patient's home—will mean a subsequent reallocation of costs from the medical to the pharmacy budget. This shift could add between \$2.50 and \$7.50 to the current \$20 to \$30 per-member-per-month drug cost, typical costs for commercial MCO members.⁷⁰ With the expected approval of dozens of new biologics in the next 5 to 10 years, increases such as these may merely signal continuously rising costs.

One estimate is that injectable medicines cost, on average, 10 times more than oral prescription drugs. From the managed care executive's point of view, it will be critical to document the advantages of biologic agents relative to traditional drug therapy in order to justify their higher costs. Identification and tracking the

use of biologic agents with reliable data collection and management systems will be key to validating claims of superior efficacy and/or cost-effectiveness.⁷⁰

At the present time, the shift that injectables are making from a medical to a pharmacy benefit will have a profound impact not only on the pharmacy budget but also on benefit design. Managing the utilization of these agents will be of keen interest to MCO executives and administrators who must ensure continued and appropriate access to biologics while they maintain affordable premiums for all of their members.

Increased Patient Cost Sharing

Increased patient cost sharing is one strategy gaining momentum in the management of MCOs. The costs for injectables are being shifted to enrolled members through use of injectable copays and coinsurance programs. For example, cost sharing can take one of several forms:

- a patient copay for injectables that is twice the cost of the most expensive oral drug copay
- a formulary tier designated specifically for biologics
- addition of coinsurance of 20% or more

The cost of biologics for one patient can run as high as \$1,500 per month, and many MCO members will be unable to meet a 20% to 40% coinsurance payment on even a short-term basis. Thus, the coinsurance scenario has obvious compliance and patient satisfaction ramifications.^{71,72}

Patient willingness to pay is largely influenced by the disease or condition with which they are faced. For example, when 100 MCO professionals were asked, “At what level of monthly out-of-pocket cost do you think patient demand begins to fall?” the responses ranged from nearly \$300 per month for therapeutic cancer versus approximately \$90 per month for asthma. Plans assume increased member willingness to pay for life-saving and disability-sparing therapies compared with other products.⁷⁰

If employers and health plans are to continue offering escalating prescription drug benefits, a fair, sustainable, and adequate level of patient cost sharing is necessary. At the same time, it is critical that quality health care not be forfeited for the goal of short-term cost savings.⁷³

A Tiered Formulary Approach

Overall, a tiered formulary approach generally incentivizes the use of lower-cost medications and may help educate consumers about their various treatment options. It also enables payers to exercise a degree of control over the utilization of high-cost products. Conversely, a tiered formulary can promote provider and consumer selection of their medication regimen on the basis of cost alone. In cases where a higher-tiered, higher-cost drug is considered most appropriate, the patient may choose not to fill the prescription, thus increasing the likelihood of noncompliance and utilization of expensive health care resources such as hospitalizations, office visits, and emergency room encounters.

FIGURE 4 Tiered Copayments for Biologics

Furthermore, due to the high cost of biologics, tiered formulary models still may only—even at the highest tier—return a small percentage of the cost of the drug back to the MCO. As shown in Figure 4, patient cost sharing in a tiered formulary environment has increased substantially, and the indications are that that trend will continue. In primary research and analysis of focus group responses from 100 managed care decision makers, 48% indicated that they currently have established a tiered formulary design for injectables and biologics, and half of those remaining anticipate developing one in the near future for this class. Injectables are generally placed in a fourth-tier position.⁷⁰

A typical 4-tier formulary design includes virtually all self-administered injectables. Under such a design, plan members are responsible for a 30% copayment with a monthly cap of \$250 per fill. Prior authorizations are required for most drugs in this tier (Figure 4).⁷²

■ Frequent Need for Injection and/or Infusion

There is a need to educate physicians, pharmacists, payers, employers, and patients on incretin mimetic therapy in particular and issues surrounding injectables in general. For example, exenatide and nearly 90% of all biopharmaceuticals require administration via injection or infusion, and 70% of these require administration by a health care professional in an ambulatory care center.⁶⁰ Exenatide is self-administered as a twice-daily SC injection. Because it works only in the presence of glucose, dosing is accurate and reliable; therefore, exenatide does not present

the challenges associated with insulin dosing.

Compared with biologics that must be infused, self-administration can yield savings for payers while reducing health plan and patient costs. Self-administration eliminates copayments and reimbursements for office visits and reduces administration costs. Compliance patterns of self-administered versus infused medications are also more robust. Increased patient satisfaction and convenience result when patients do not have to visit a medical facility to be compliant with their medication regimen. SC administration versus intramuscular injection is also an advantage with the new incretin mimetics for type 2 diabetes.⁷⁰

Distribution of Injectables Through Specialty Pharmacy Companies

As more expensive biologic agents are approved for an increasing number of diseases, managed care will likely opt

for a carved-out or injectables-only benefit option for its employer customers. Another strategy that is gaining momentum is the use of specialty pharmacy providers (SPPs). An SPP receives the prescription and fills it within 72 hours, delivering it directly to either the health care provider or patient. The health plan is then billed for the medication. These companies join forces with managed care to share risk and control costs. Cost control is achieved by

- reduced provider need for inventory of high-priced drugs
- reduced provider administrative costs
- reduced costs to members and employers through streamlined distribution channels

SPPs may also provide educational resources in disease areas where managed care providers may be less experienced. They may also have sophisticated, integrated systems in place that enable them to collect data on utilization and cost. Many employ comprehensive disease management programs that enable them to document patient outcomes and engage in outreach to increase compliance.^{72,74}

Through a combination of greater purchasing power, just-in-time delivery, and strong oversight, specialty pharmacy vendors have reduced commercial plans' acquisition costs for biologics to a level 14% to 17% below average wholesale price. Additionally, the use of SPPs for management of injectables is decidedly on the rise, with 65% of plans utilizing these specialized services in the fall of 2003 and a projected 87% of them contracting with SPPs within the next 18 months.⁷⁰

All of these issues surrounding biologics point to the need for a well-designed and effective pharmacy benefit that balances drug access, quality, and cost to provide maximum value to both patients and payers.

Conclusion

How Managed Care Will Adapt to Specialty Pharmaceuticals

The managed care marketplace is driven by cost and quality considerations in achieving optimal patient outcomes. Currently, the increase in cost shifting to patients and cost concerns of the purchaser appear to dominate the clinical outcomes discussion. Some patients are choosing drugs based on their copay levels. The focus should remain on the reduction of the disability associated with chronic disease, a difficult challenge to overcome in a progressive disease state such as diabetes.

To effectively manage costs and provide patients with quality care, MCOs must recognize and adequately plan for the expanding availability of biologics. This goal may be achieved within the confines of a formulary based on good clinical evidence of efficacy and cost savings in the longer term. High-quality pharmacoeconomic studies are fundamental to accurate and far-sighted clinical decision making that is based on the value and the price of a therapy.

Without this knowledge and foresight, plans may see runaway costs due to suboptimal pharmaceutical treatment options for patients with type 2 diabetes and other chronic diseases. Providers must be vigilant in monitoring their diabetes patients' glycemic control, and when it reaches unacceptable levels, they must have access to new therapies with proven efficacy. With the advent of more costly injectable biologics, MCO executives and providers will require extensive education to understand and integrate these advances in their treatment regimens and formulary decisions.

In terms of incretin mimetics, it is likely that distribution channels will be similar to those of insulin and interferon. Incretin mimetics should be readily available but may require prior authorization from the MCO. Prudent management of potentially high-cost biologics such as the incretin mimetics underscores the importance of identifying optimal candidates for this type of therapy, and requirement of a prior authorization generally ensures that the correct patient is prescribed the optimal drug.

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Incretin Mimetics: Promising New Therapeutic Options in the Treatment of Type 2 Diabetes

Medical Outcomes Management, Inc. is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. A total of 0.10 CEU (1.0 contact hour) will be awarded and a continuing education statement will be sent 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 Program Evaluation form. ACPE Universal Program No. 078-999-05-001-H04. (Release date: September 1, 2005; Expiration date: January 12, 2008)

Continuing Education for this program is processed solely through the AMCP.org Online Learning Center site at www.amcp.org (Learning Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, "Incretin Mimetics: Promising New Therapeutic Options in the Treatment of Type 2 Diabetes," on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: There will be a \$10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: Incretin Mimetics: Promising New Therapeutic Options in the Treatment of Type 2 Diabetes

1. Insulin resistance
 - a. occurs when insulin cannot be properly or effectively utilized by peripheral tissues.
 - b. can be due to inactivity, obesity, and genetic factors.
 - c. can be part of the insulin resistance syndrome that increases the risk for CAD, morbidity, and mortality.
 - d. All of the above
2. The UKPDS 35 documented that
 - a. any reduction in A1c reduces diabetic complications.
 - b. each 1% reduction in A1c is associated with a 21% risk reduction for any diabetic end point.
 - c. the lowest risk for the development of complications is among those with an A1c <6%.
 - d. All of the above
3. The following percentage of Americans with type 2 diabetes have an A1c above 8%:
 - a. 12%
 - b. 25%
 - c. 37%
 - d. 46%
4. Postprandially, GLP-1 exhibits all of the following with the exception of
 - a. the ability to restore the first-phase insulin response.
 - b. suppression of hunger.
 - c. suppression of glucagons.
 - d. reduction in beta-cell index.

5. Postprandially, exenatide exhibits all of the following with the exception of
 - a. a reduction in plasma glucagons.
 - b. accelerated gastric emptying.
 - c. a reduction in plasma glucose.
 - d. an increase in plasma insulin levels.
6. Dozens of biologic agents will soon be entering the marketplace to treat a wide variety of illnesses. By the end of 2006, spending on these agents is estimated to be
 - a. \$100 million.
 - b. \$4 billion.
 - c. \$25 billion.
 - d. \$40 billion.
7. Patient cost sharing can take one of the following forms:
 - a. a copay for injectables that is double the cost of the most expensive oral drug copay
 - b. a formulary tier reserved exclusively for biologics
 - c. addition of coinsurance of 20% or more
 - d. All of the above
8. A tiered-formulary approach achieves all of the following except
 - a. promoting the use of lower-cost medications.
 - b. ensuring the capture of cost and utilization data.
 - c. educating consumers about various treatment options.
 - d. enabling payers to exercise control over the utilization of high-cost drugs.
9. SPPs and managed care plans share risks and control costs of injectable drugs through all of the following strategies except
 - a. reduced provider need for inventory of biologics.
 - b. reduced provider administrative costs.
 - c. streamlined distribution channels.
 - d. risk sharing with large self-insured employer groups.
10. Through the utilization of greater purchasing power, fast delivery, and active oversight, SPPs have reduced managed cares' acquisition costs for biologics by
 - a. 5% to 7%.
 - b. 9% to 12%.
 - c. 14% to 17%.
 - d. more than 25%.

**To complete this activity, go to www.amcp.org (Learning Center/Online CE),
where you will access the posttest and evaluation form.**

NOTES

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