

Late-Breaking Clinical Developments
for Managed Markets

MANAGED CARE CONSULTANT®


First
REPORT®

Type 2 Diabetes: Understanding Disease Impact and Evaluating Emerging Treatment Options

***A review of the outcomes related to glycemic control
and the potential for newer agents to aid in
improved management of type 2 diabetes***



Jointly sponsored by Princeton Media Associates, Program in Medicine Division
and the University of Cincinnati College of Medicine

July 2006

Type 2 Diabetes: Disease Impact and Treatment Options

CPE ACCREDITATION



Princeton Media Associates, Program in Medicine Division is accredited by the Accreditation Council for Pharmacy Education as a Provider of continuing pharmacy education (ACPE Provider #452) and complies with the Criteria for Quality and Interpretive Guidelines. This activity is approved for 1 hour credit (0.1 CEU) of continuing pharmacy education (ACPE #452-999-06-001-H01).

Any participant wanting to file a grievance with respect to any aspect of a continuing pharmacy education activity sponsored or cosponsored by Princeton Media Associates, Program in Medicine Division may contact the Program Coordinator in writing. The Program Coordinator will review the grievance and respond within 30 days of receiving the written statement. If the participant is unsatisfied with the response, an appeal to the Vice President of Educational Services may be made for a second level of review.

CME ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Cincinnati College of Medicine and Princeton Media Associates, Program in Medicine Division. The University of Cincinnati College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati College of Medicine designates this activity for 1 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

TARGET AUDIENCE

This activity is designed for physicians and pharmacists within managed markets.

STATEMENT OF NEED

Type 2 diabetes affects more than 20 million people in the United States. Type 2 diabetes and related complications lead to an estimated 17 million hospitalization days per year, and the economic impact of the disease is estimated to exceed \$130 billion annually. Patients who fail to maintain tight blood glucose levels have an elevated risk of long-term comorbidities such as kidney disease, myocardial infarction, and stroke, which have the potential to exacerbate both the health of the patient and the economic burden of the disease. As newer therapies emerge, it is necessary to provide an update on the latest safe and effective methods of glucose control, including the potential for novel therapies to improve patient quality of life and reduce healthcare resource use.

LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Articulate the growing clinical and economic burden of type 2 diabetes
- Outline the impact of effective type 2 diabetes management on patient health and healthcare costs
- Summarize data regarding the safety and efficacy of traditional and new type 2 diabetes pharmacotherapies
- Review the unmet needs of conventional therapies
- Describe the potential role of 2 new type 2 diabetes medications

Release Date: May 30, 2006; Expiration Date: June 20, 2007

There is no fee associated with this activity.

To be eligible for documentation of credit, participants must read all monograph content, complete the 10-question post-test with a score of 70% or better, and complete the evaluation form. Please e-mail info@princetoncme.com or call 609-371-1137 if you have questions or need additional information.

[CLICK HERE TO TAKE POST-TEST ONLINE](#)

FACULTY

Lawrence Blonde, MD, FACP, FACE

Director

Ochsner Diabetes Clinical Research Unit

Department of Endocrinology, Diabetes,
and Metabolic Diseases

Associate Internal Medicine Residency Program Director

Ochsner Clinic Foundation

New Orleans, Louisiana

Jeremy Gleeson, MD, FACP, CDE

Chief Quality Officer

Associate Medical Director

Chair, Division of Endocrinology

Lovelace Sandia Health Systems

Albuquerque, New Mexico

INDEPENDENT CLINICAL REVIEWER

Mark E. Williams, MD, FACP

Associate Professor of Medicine

Harvard Medical School

Staff Nephrologist

Clinical Investigator

Section on Clinical Research

Joslin Diabetes Center

Boston, Massachusetts

DISCLOSURE INFORMATION

In accordance with the disclosure policies of Princeton Media Associates, Program in Medicine Division and the University of Cincinnati College of Medicine, the effort is made to ensure balance, independence, objectivity, and scientific rigor in all educational activities. These policies include resolving all conflicts of interest between faculty and commercial interests that might otherwise compromise the goal and educational integrity of this activity. All faculty members participating in this activity have disclosed all relevant financial relationships with commercial interests. The planners of this activity have reviewed these disclosures and have determined that the faculty relationships are not inappropriate in the context of their respective presentations and are not inconsistent with the educational goals and integrity of the activity.

The faculty reported the following:

Dr. Blonde: Grant/research support—Amylin Pharmaceuticals, Inc, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, MannKind Corporation, Novartis Pharmaceuticals, Novo Nordisk, Pfizer Inc, sanofi-aventis U.S.; Consultant and Speaker—Abbott Laboratories, Amylin Pharmaceuticals, Inc, Eli Lilly and Company, GlaxoSmithKline, Lifescan, Inc, Merck & Co., Inc/Schering-Plough, Novartis Pharmaceuticals, Pfizer Inc, sanofi-aventis U.S.; Consultant—AstraZeneca; Speaker—Takeda Pharmaceuticals, Wyeth

Dr. Gleeson: Speaker with honorarium—AstraZeneca, GlaxoSmithKline, Merck & Co., Inc, Novo Nordisk, sanofi-aventis U.S.

Dr. Williams has disclosed he has no relevant financial relationships with any commercial interests.

Planning Committee Kristin Dickie, Rosemary Hodgson, and Deborah Neveleff, Princeton Media Associates; Randy Robbin, Princeton Media Associates, Program in Medicine Division; and Kay Weigand, University of Cincinnati College of Medicine, Office of Continuing Education, have disclosed they have no relevant financial relationships with any commercial interests.

The University of Cincinnati College of Medicine and Princeton Media Associates Program in Medicine Division require faculty to inform participants whenever off-label/unapproved uses of drugs or devices are discussed in their presentation. The faculty has disclosed that no off-label/unapproved uses of drugs or devices will be discussed.

GRANT SUPPORT

Supported by an educational grant from Amylin Pharmaceuticals, Inc, and Eli Lilly and Company

Type 2 Diabetes: Understanding Disease Impact and Evaluating Emerging Treatment Options

Of the 20.8 million Americans estimated to have diabetes, 90% to 95% have type 2 diabetes.¹ This *First Report*[®], which is based on a recent continuing education teleconference series, will provide important information about effective methods of improving diabetes management through a review of the growing clinical and economic burden of type 2 diabetes, the impact of effective diabetes management on patient health and healthcare costs, the safety and efficacy of various pharmacotherapies, the limited success of conventional treatments, and the potential of new medications to improve outcomes.

CLINICAL AND ECONOMIC BURDEN

Between 1994 and 2004, the prevalence of diabetes in the US population increased dramatically. By 2004, the majority of the states had diabetes prevalence rates of 6% or greater.² According to the Centers for Disease Control and Prevention, in the United States approximately 7% of the total population, nearly 10% of adults, and more than 20% of individuals age 60 and older, have diabetes.¹

Diabetes is associated with substantial morbidity and mortality. Comorbidities include microvascular conditions such as nephropathy and retinopathy; neuropathy; and macrovascular conditions such as myocardial infarction (MI), congestive heart failure, stroke, and peripheral arterial disease. Diabetes is associated with a 2-fold increase in mortality risk and a 2- to 4-fold increase in risk of death from heart disease.¹

The US expenditures attributable to diabetes reached \$132 billion in 2002.³ Of these costs, 42% were associated with institutional care, 30% with indirect costs (including premature mortality, absenteeism, and loss of productivity), 15% with

outpatient care, and 13% with medication and supplies.³ By 2020, costs are projected to reach \$192 billion annually.³

PATHOPHYSIOLOGY

Patients with type 2 diabetes have at least a relative defect in the ability to secrete insulin from their beta cells, and the vast majority also have a resistance to the action of insulin. The beta-cell defect generally progresses over time. In the United Kingdom Prospective Diabetes Study (UKPDS), beta-cell function had decreased to about 50% of normal at the time of diagnosis of diabetes and continued to decline despite therapy with diet, metformin, or sulfonylureas.⁴ As the severity in loss of beta-cell function progresses, so does the severity of the disease.

Another component of the pathophysiology of type 2 diabetes is an abnormality in glucagon secretion. In response to a high-carbohydrate meal, individuals without diabetes exhibit a prompt increase in insulin secretion and a decline in glucagon secretion. Both decrease hepatic glucose production by the liver in the postprandial period.⁵ As a result, there is only a modest increase in glucose in response to the meal. In contrast, individuals with diabetes have a delayed and diminished insulin response to a carbohydrate meal; glucagon does not decline and may even increase, and as a result there is an excessive glycemic excursion.⁵ An infusion of insulin can remediate the prandial plasma insulin profile but will not correct the glucagon abnormality.

In nondiabetic individuals, an oral glucose load results in an insulin response that is up to 3 times greater than when the same subjects are given an intravenous glucose infusion to exactly match the plasma glucose levels seen with the oral load. This phenomenon, termed the “incretin effect,” is

TELECONFERENCE PRESENTER

Lawrence Blonde, MD, FACP, FACE, Director, Ochsner Diabetes Clinical Research Unit, Department of Endocrinology, Diabetes, and Metabolic Diseases, Associate Internal Medicine Residency Program Director, Ochsner Clinic Foundation, New Orleans, Louisiana

defined as the difference in insulin response to oral versus intravenous glucose loads.⁶ In patients with type 2 diabetes, the incretin effect is diminished or absent.

Two gastrointestinal peptides that have been identified as incretins are glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). Secretion of both incretins appears to be impaired in type 2 diabetes. 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 type 2 diabetes. GLP-1 enhances insulin secretion and diminishes glucagon secretion in a glucose-dependent manner (generally enhances insulin secretion and decreases glucagon secretion only when glucose levels are above normal). GLP-1 also slows gastric emptying (which is often accelerated in type 2 diabetes), enhances satiety, and decreases food intake.

Evidence of diabetes-related GLP-1 deficiency was obtained from a study in which 54 type 2 diabetes patients, 33 matched control subjects with normal glucose tolerance, and 15 unmatched subjects with impaired glucose tolerance had GLP-1 levels measured during a 4-hour mixed-meal test. A significant GLP-1 deficiency 60 minutes after the meal was noted in patients with type 2 diabetes compared to nondiabetic participants ($P=.024$).⁷ Patients with impaired glucose tolerance demonstrated a similar but not statistically significant GLP-1 deficiency.

BENEFITS OF IMPROVED DIABETES CONTROL

Several studies have demonstrated that lowering hemoglobin A1C (A1C) reduces diabetes complications. The Diabetes Control and Complications Trial (DCCT), which randomized 1441 type 1 diabetes patients to receive either intensive or conventional insulin therapy for an average of 6.5 years between 1983 and 1993, found that an improvement in A1C from 9.1% in the conventional group to 7.3% in the intensive treatment group was associated with a 63% decrease in retinopathy, a 54% decrease in nephropathy, and a 60% decrease in neuropathy.⁸ Another randomized study of 110 insulin-treated type 2 diabetes patients found that, compared to conventional therapy subjects, intensively treated subjects had a lower A1C (7.1% compared to 9.4%), a 69% decrease in retinopathy, and a 70% decrease in nephropathy.⁹ The UKPDS reported that a reduction in A1C from 7.9% to 7% with intensive pharmacologic therapy compared to conventional diet therapy was associated with a 17% to 21% decrease in retinopathy and a 24% to 33% decrease in nephropathy.¹⁰

In the Steno-2 trial, patients with type 2 diabetes and microalbuminuria were randomized into 2 groups: one group received conventional treatment in accordance with national guidelines, and the other received intensive treatment targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, as well as secondary prevention of cardiovascular disease with aspirin.¹¹ The study reported a 53% reduction in the occurrence of macrovascular diseases, including cardiovascular death, nonfatal MI, coronary artery bypass graft, percutaneous transluminal coronary angiography, nonfatal stroke,

amputation, and bypass, as well as a 60% reduction in microvascular diseases, in the intensive treatment group.¹¹ This study demonstrated the importance of treating the often accompanying hypertension and dyslipidemia in type 2 diabetes patients as well as the benefits of aspirin and treatment of microalbuminuria.

A recent report from the DCCT-Epidemiology of Diabetes Interventions and Complications researchers provided follow-up information many years after the end of the DCCT. Compared to the conventional group, type 1 diabetes patients assigned to intensive treatment in the DCCT had a 42% decrease in risk for any cardiovascular outcome and a 57% reduction in the risk for nonfatal MI, stroke, or death from cardiovascular disease, even though during most of the follow-up period there was little difference in the 2 groups' A1C levels.¹² 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 the treatment is begun, the greater the likely benefit because of an apparent metabolic memory of good and bad control.

Furthermore, in an epidemiologic analysis of the UKPDS, researchers found that every 1% decrement in A1C yielded a 21% reduction in diabetes-related death, a 14% reduction in MI, and a 37% reduction in microvascular disease.¹³

Since better glycemic control is associated with improved clinical outcomes, lowering A1C may also reduce healthcare costs. UKPDS researchers calculated that the intensive therapy program cost £695 per patient but was associated with a £957 decreased cost of complications.¹⁴ An observational study by Wagner et al compared patients who exhibited a 1% decrease in A1C in the first or second year and maintained that decrease through a third year of the study to patients who did not have an improved A1C. In the subsequent 3 years, mean total healthcare costs were reduced by \$685 to \$950 annually in the improved A1C group.¹⁵

Finally, data support that diabetes control leads to better quality of life. A study by Testa and Simonson compared placebo and sulfonylurea treatment for 16 weeks and found that compared to patients receiving placebo, patients who received pharmacologic treatment not only improved their A1C levels but also reported marked improvement in ratings of overall health, mental health, cognitive function, perceived health, and symptom distress.¹⁶

NONPHARMACOLOGIC TREATMENT AND EDUCATION

Because diabetes is a self-managed disease, diabetes education and self-management training are crucial components of optimal diabetes care and have been associated with enhanced patient outcomes. For example, patients who entered the Ochsner Diabetes Education Program with a baseline A1C of 8.6% were able to reduce their A1C to approximately 7% after 3 months and maintain that improvement through 6 months ($P<.001$).¹⁷

Type 2 Diabetes: Disease Impact and Treatment Options

Table. Traditional Antihyperglycemic Therapy Currently Used in the United States

Oral Agents	Insulin
Nonsulfonylurea Secretagogues	Basal
Repaglinide	NPH
Nateglinide	Glargine
Alpha-Glucosidase Inhibitors	Detemir
Acarbose	Prandial
Meglitol	Regular
Thiazolidinediones	Aspart
Rosiglitazone	Glulisine
Pioglitazone	Lispro
Sulfonylureas	Other Formulations
Glimepiride	Premixed Human Insulins
Glipizide/Glipizide GITS	Premixed Analog Insulins
Glyburide	
Metformin	

GITS = gastrointestinal therapeutic system.

Nutrition therapy and appropriately prescribed physical activity are cornerstones of diabetes management. In a prospective, randomized, controlled trial involving 179 patients, Franz et al found that compared to patients with no nutrition education, patients with either 1 or 3 visits to a dietitian were able to significantly improve their A1C levels ($P < .05$).¹⁸ A meta-analysis of the effects of exercise on glycemic control and body mass examined 12 aerobic and 2 resistance training studies; A1C was 7.65% in the exercise groups compared to 8.31% in the control groups, even though postintervention weight did not differ significantly.¹⁹

TRADITIONAL TYPE 2 DIABETES PHARMACOTHERAPY

Despite the value of lifestyle measures, most patients with type 2 diabetes will require pharmacotherapy in addition to lifestyle measures in order to achieve glycemic goals.

Several oral monotherapeutic agents, as well as a variety of subcutaneous insulins are Food and Drug Administration (FDA)-approved for the treatment of type 2 diabetes. These agents are listed in the [Table](#). While all of these agents serve to improve glycemic control, they work through various mechanisms of action, including decreasing hepatic glucose production, enhancing endogenous insulin secretion, and enhancing insulin sensitivity. Insulin choice is guided by whether the patient lacks an adequate basal effect, an adequate postprandial effect, or both.

In clinical trials and in clinical practice, oral antidiabetic agents have proven effective at reducing A1C levels in type 2 diabetes patients. In a double-blind, dose-response study in which 451 subjects were randomized to receive an 11-week course of placebo or metformin, metformin was shown to reduce A1C by up to 2% compared to placebo.²⁰ In 2 prospective, randomized, double-blind, placebo-controlled trials involving 347 subjects, the Glipizide Gastrointestinal Therapeutic System (GITS) Study Group found that glipizide GITS reduced A1C by 1.5% to 1.8% compared to placebo.²¹

Goldberg et al randomized 304 patients to receive either placebo or glimepiride over 14 weeks and found that, compared to placebo, glimepiride reduced A1C by up to 1.9%.²² In a double-blind clinical trial in which 408 patients were randomized to receive placebo or pioglitazone administered once a day for 26 weeks, researchers found that, compared to placebo, pioglitazone reduced A1C by 1% to 1.6%.²³ Lebovitz et al randomized 493 patients to receive rosiglitazone or placebo for 26 weeks, and found that rosiglitazone reduced A1C by 1.2% to 1.5% relative to placebo.²⁴ A 1-year, randomized, double-blind study of outpatients with type 2 diabetes found that repaglinide reduced A1C by 1% from baseline.²⁵ Acarbose has been shown to reduce A1C by 0.4% to 1.1% from baseline.^{26,27} A randomized, double-blind, placebo-controlled study conducted in 289 patients found that nateglinide reduced A1C by 0.45% to 0.64% compared to placebo.²⁸

Oral agents, like all medications, can be associated with some adverse effects.²⁹ The sulfonylureas and nonsulfonylurea secretagogues can cause hypoglycemia. Weight gain may occur with the use of sulfonylureas, nonsulfonylurea secretagogues, and thiazolidinediones. Thiazolidinedione use can increase the risk of edema, and in rare cases, congestive heart failure.²⁹ Metformin and the alpha-glucosidase inhibitors can have gastrointestinal side effects, and metformin use may cause lactic acidosis, although the risk is extremely low as long as metformin is prescribed as recommended and is not prescribed to patients with renal insufficiency or other conditions that increase the risk for lactic acidosis.²⁹

Insulin is the pharmacologic agent with the greatest glucose-lowering capacity. Insulin use may be associated with episodes of hypoglycemia. Weight gain may also occur with insulin use, but can be diminished by combining insulin with metformin.

Attainment of Glycemic Goals with Conventional Therapy.

Unfortunately, despite the effectiveness of the oral antidiabetic agents and insulin, most type 2 diabetes patients do not achieve recommended glycemic goals. Saaddine et al reviewed national population-based, serial cross-sectional surveys—the National Health and Nutrition Examination Survey (1988-1994 and 1999-2002) and the Behavioral Risk Factor Surveillance System (1995 and 2002)—and found a non-significant decrease in the number of patients with A1C >9% and a nonsignificant increase in patients with A1C <7%.³⁰ Furthermore, in the most recent of these surveys, almost 60% of patients had not achieved an A1C <7%, and 20% had an A1C >9%.³⁰ Similarly, in 2005, the American Association of Clinical Endocrinology's State of Diabetes in America report noted that of more than 157,000 patients with type 2 diabetes in 39 states, 67% had A1C values $\geq 6.5\%$.³¹

There are a number of reasons that most type 2 diabetes patients do not achieve A1C goals, including the failure of clinicians to adopt a treat-to-target approach, a frequent lack of optimal systems of healthcare delivery, and failure of patients to adhere fully to lifestyle and pharmacologic treatments.

While current therapies should be associated with better results, these treatments do have a number of limitations. Adverse events, such as weight gain noted above, can exacerbate comorbidities and inhibit adherence. In addition, most

therapies fail to adequately control postprandial hyperglycemia, and wide glycemic fluctuations can persist despite treatment.³² Finally, most therapies fail to maintain long-term glycemic control.³³ In the UKPDS, after initial improvement, A1C levels increased over time, regardless of the monotherapy used.³³ In this study, gradual loss of glycemic control in patients taking a sulfonylurea or metformin was associated with progressive loss of beta-cell function.³⁴ Earlier and more aggressive treatment that attains and maintains glycemic goals as soon as possible may better preserve beta-cell function and lead to more durable control of glycemia.

Oral Combination Therapy. Combining 2 or more oral agents with different and complementary mechanisms of action can result in improved glycemic control. Combination therapy should be considered for type 2 diabetes patients who cannot achieve a target A1C level on monotherapy and for patients who present initially with an A1C \geq 8.5% to 9%.

One randomized, controlled trial showed that sulfonylurea and metformin combination therapy yielded an average A1C level of 7.1% compared to 8.7% with sulfonylurea alone.³⁵ A double-blind study reported that sulfonylurea and pioglitazone combination therapy yielded an average A1C level of 8.7% compared to 9.9% with sulfonylurea alone.³⁶ In both of these trials, combining a secretagogue with a sensitizer resulted in improved glycemia. Clinicians can combine 2 sensitizers since metformin has most of its glycemic effect by decreasing hepatic glucose production and the thiazolidinediones enhance insulin sensitivity primarily in muscle and adipose tissue. A randomized, placebo-controlled trial comparing the addition of rosiglitazone or placebo in patients not at goal on metformin monotherapy resulted in a placebo-subtracted A1C reduction of 1.2% for subjects receiving metformin plus 8 mg of rosiglitazone.³⁷

To enhance ease of administration and adherence, a number of single-pill combinations are now available, including glyburide and metformin; glipizide and metformin; rosiglitazone and metformin; pioglitazone and metformin; and rosiglitazone and glimepiride.

NEW PHARMACOTHERAPIES

New therapies recently approved or still in development may be able to address some of the limitations of traditional therapies. Newer therapeutic options include inhaled insulin and incretin-related therapies.

Inhaled Insulin. Insulin human (rDNA origin) inhalation powder is a dry powder formulation delivered by an oral inhalation system. Inhaled insulin is more quickly absorbed and has a more rapid glucose-lowering effect than subcutaneously injected regular human insulin. Its onset of action and glucose-lowering effect are similar to rapid-acting insulin analogues, but its duration of action is similar to regular human insulin.³⁸ Insulin human inhalation powder, approved in January 2006, is the first FDA-approved inhaled insulin.³⁸ Several other inhaled insulin products are currently in the development process. In patients with type 1 diabetes, inhaled insulin should be used in regimens that include a longer-acting or basal insulin. In patients with type 2 diabetes, it can be used as monotherapy or in combination with oral agents or longer-acting insulins.

In clinical trials, inhaled insulin provided improved A1C control comparable to subcutaneously injected regular human insulin. A 6-month, randomized trial examined type 2 diabetes patients treated with premeal inhaled insulin plus a bedtime dose of ultralente insulin compared to those treated with at least 2 daily injections of subcutaneous mixed regular/NPH insulin.³⁹ While A1C decreased similarly in the 2 treatment groups, the percentage of patients who achieved an A1C $<$ 7% was greater in the inhaled insulin group (47% vs 32%).³⁹ A 12-week, active-control, open-label trial of 298 patients who did not achieve A1C goals on 2 oral agents compared placebo to switching patients to inhaled insulin or adding inhaled insulin to the oral agents. Reduction in A1C values was 0.2% in the placebo group, 1.4% in the inhaled insulin group, and 1.9% in the inhaled insulin plus oral agents group.⁴⁰ Inhaled insulin, either alone or combined with oral agents, resulted in decreased fasting plasma glucose (-23 mg/dL on inhaled insulin monotherapy, -53 mg/dL on combination therapy), but increased body weight compared to oral agents alone (2.8-kg increase with inhaled insulin monotherapy, 2.7-kg increase with combination therapy).⁴⁰

Inhaled insulin is contraindicated in patients who smoke or who have discontinued smoking less than 6 months prior to starting therapy and in patients with unstable or poorly controlled lung disease.⁴¹ Inhaled insulin is also not recommended in patients with underlying lung disease, such as asthma or chronic obstructive pulmonary disease, because the safety and efficacy of inhaled insulin in this population have not been established.⁴¹ Hypoglycemia is the most commonly reported adverse event with all insulin therapy, including inhaled insulin. In clinical trials, treatment with inhaled insulin was associated with very small, nonprogressive mean declines in pulmonary function relative to comparator treatments, and respiratory adverse events included cough, which tended to occur within seconds to minutes after inhalation. The incidence of cough decreased with continued inhaled insulin use.

Incretin-Related Therapies. The incretin GLP-1 has a number of antihyperglycemic effects, including increasing endogenous insulin secretion and decreasing glucagon secretion, both in a glucose-dependent manner, slowing of gastric emptying, and increasing satiety.⁴²

Clinical use of native GLP-1 would be limited because it is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which breaks down GLP-1 within minutes. Continuous sub-

Despite the value
of lifestyle measures,
most patients with
type 2 diabetes will
require pharmacotherapy
in addition to lifestyle
measures in order to
achieve glycemic goals.

Type 2 Diabetes: Disease Impact and Treatment Options

cutaneous infusion of GLP-1, an unattractive therapeutic approach, would be required for its clinical use.^{43,44} Other approaches to achieving GLP-1 effects 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.

Incretin mimetics have a much longer half-life than GLP-1 and are administered via subcutaneous injection. The first FDA-approved GLP-1-related agent, exenatide, is a synthetic analogue of exendin-4 and a GLP-1 receptor agonist that binds to GLP-1 receptors.⁴⁵ Because it remains in plasma for up to 10 hours following subcutaneous injection, exenatide can be administered twice daily.⁴⁵ It is advised that exenatide should be administered within 60 minutes of 2 major meals that are at least 6 hours apart. Exenatide mimics many of the properties of GLP-1. In a 2003 study, exenatide was found to increase insulin and significantly reduce fasting ($P<.05$) and postprandial ($P<.0001$) glucose concentrations in patients with type 2 diabetes.⁴⁷

In 3 large phase 3 pivotal registration trials, exenatide 5 mcg or 10 mcg injected subcutaneously twice daily was compared to placebo in type 2 diabetes patients who had not achieved adequate glycemic control despite therapy with metformin and/or a sulfonylurea. From a baseline A1C of 8.2% to 8.6%, exenatide produced dose-dependent declines in A1C levels in all 3 studies.⁴⁸⁻⁵⁰ The 10-mcg dose produced a decrease in fasting plasma glucose, an average 1% reduction in A1C, and a 1.1-kg weight reduction when compared to placebo in these studies.⁴⁸⁻⁵⁰

A study by Heine et al compared the addition of exenatide or insulin glargine in type 2 diabetes subjects suboptimally controlled with metformin and a sulfonylurea. Exenatide and insulin glargine achieved similar reductions in A1C.⁵¹ Patients on exenatide experienced a weight loss of 2.3-kg, compared with a 1.8-kg weight gain in insulin-treated patients, but gastrointestinal symptoms were greater in the exenatide group.⁵¹ Individuals who received exenatide in addition to metformin

experienced no greater occurrence of hypoglycemia than those on placebo, which is what one would anticipate with an agent that enhances insulin secretion in a glucose-dependent manner.⁴⁸ Hypoglycemia risk increased when exenatide was added to a sulfonylurea.^{49,52} Therefore, clinicians should consider initial reduction of the sulfonylurea dose prior to adding exenatide to sulfonylureas either alone or in combination with metformin.

Nausea is the most frequently observed adverse event associated with exenatide.⁵³ In a 30-week, double-blind, placebo-controlled study of 733 subjects, twice-daily doses of 5 mcg and 10 mcg of exenatide were associated with nausea related discontinuation rates of 2% and 4%, respectively.⁵² Most episodes are mild to moderate in intensity, are intermittent, and tend to decrease over time with continuation of therapy.⁵²

Another incretin mimetic, liraglutide, is a GLP-1 analogue that modifies the GLP-1 molecule so that it lasts longer in plasma. This agent is currently in phase 3 trials. Incretin enhancers, or DPP-4 inhibitors, are still under investigation or awaiting an FDA approval decision. These agents block the enzyme that breaks down GLP-1 and enhance endogenous GLP-1 levels. Two incretin enhancers, vildagliptin and sitagliptin, are awaiting an FDA approval decision; several others are in Phase 2 or 3 clinical trials.

CONCLUSION

Type 2 diabetes has reached epidemic proportions, resulting in a considerable clinical and economic burden. Unfortunately, most patients with diabetes do not achieve treatment goals, and conventional treatments are often associated with weight gain, postprandial hyperglycemia, hypoglycemia, and progressive loss of glycemic control, beta-cell function, and mass. However, recently developed therapies, and others still in development, may address some of these presently unmet needs and help a greater number of patients achieve desired treatment goals. **n**

References

1. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf. Accessed May 15, 2006.
2. Behavioral Risk Factor Surveillance System. Centers for Disease Control and Prevention. Available at: <http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/> and <http://www.cdc.gov/diabetes/statistics/prev/state/>. Accessed January 20, 2006.
3. Hogan P, Dall T, Nikolov P, American Diabetes Association. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26:917-932.
4. Saltiel AR. New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell*. 2001;104:517-529.
5. Unger RH. Glucagon physiology and pathophysiology. *N Engl J Med*. 1971;285:443-449.
6. Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986;63:492-498.
7. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86:3717-3723.
8. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329:977-986.
9. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117.
10. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
11. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.
12. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. DCCT-EDIC Study Research Group. *N Engl J Med*. 2005;353:2643-2653.
13. Stratton IM, Adler AI, Beil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
14. Gray A, Rajjou M, McGuire A, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United

- Kingdom Prospective Diabetes Study Group. *BMJ*. 2000;320(7246):1373-1378.
15. Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. Effect of improved glycemic control on health care costs and utilization. *JAMA*. 2001;285(2):182-189.
 16. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA*. 1998;280:1490-1496.
 17. 62nd Scientific Sessions of the American Diabetes Association. June 14-18, 2002; San Francisco, Calif.
 18. Franz MJ, Monk A, Barry B, et al. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc*. 1995;95:1009-1017.
 19. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus. *JAMA*. 2001;286:1218-1227.
 20. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med*. 1997;103:491-497.
 21. Simonson DC, Kourides IA, Feinglos M, Shamoon H, Fischette CT. Efficacy, safety, and dose-response characteristics of glipizide gastrointestinal therapeutic system on glycemic control and insulin secretion in NIDDM. Results of two multicenter, randomized, placebo-controlled clinical trials. The Glipizide Gastrointestinal Therapeutic System Study Group. *Diabetes Care*. 1997;20:597-606.
 22. Goldberg RB, Holvey SM, Schneider J. A dose-response study of glimepiride in patients with NIDDM who have previously received sulfonylurea agents. The Glimepiride Protocol #201 Study Group. *Diabetes Care*. 1996;19:849-856.
 23. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. *Diabetes Care*. 2000;23:1605-1611.
 24. Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI, Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:280-288.
 25. Wolfenbittel BH, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Dutch and German Repaglinide Study Group. *Diabetes Care*. 1999;22:463-467.
 26. Coniff RE, Shapiro JA, Seaton TB, Hoogwerf BJ, Hunt JA. A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes. *Diabetes Care*. 1995;18(7):928-932.
 27. Coniff RE, Shapiro JA, Robbins D, et al. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM. A placebo-controlled dose-comparison study. *Diabetes Care*. 1995;18(6):817-824.
 28. Hanefeld M, Bouter KP, Dickinson S, Guitard C. Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care*. 2000;23:202-207.
 29. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA*. 2002;287(3):360-372.
 30. Saaddine JB, Cadwell B, Gregg EW, et al. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988-2002. *Ann Intern Med*. 2006;144:465-474.
 31. The American Association of Clinical Endocrinologists. State of Diabetes in America: Striving for Better Control. Available at: http://www.stateofdiabetes.com/state_compare.htm. Accessed March 14, 2006.
 32. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.
 33. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-865.
 34. UK Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. UK Prospective Diabetes Study Group. *Diabetes*. 1995;44:1249-1258.
 35. DeFronzo R, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med*. 1995;333:541-549.
 36. Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med*. 2001;111:10-17.
 37. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*. 2000;283:1695-1702.
 38. FDA News. FDA Approves First Ever Inhaled Insulin Combination Product for Treatment of Diabetes. Available at: <http://www.fda.gov/bbs/topics/news/2006/NEW01304.html>. Accessed May 17, 2006.
 39. Hollander PA, Blonde L, Rowe R, et al. Efficacy and safety of inhaled insulin (exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care*. 2004;27:2356-2362.
 40. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2005;143:548-558.
 41. Exubera [package insert]. New York, NY: Pfizer Inc.; 2006.
 42. Glucagon and the glucagon-like peptides. Available at: <http://www.glucagon.com>. Accessed July 3, 2006.
 43. Kieffer TJ, Hanener JF. The glucagon-like peptides. *Endocr Rev*. 1999;20:876-913.
 44. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH₂-terminus in type II diabetic patients and in healthy subjects. *Diabetes*. 1995;44:1126-1131.
 45. Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept*. 2004;117:77-88.
 46. Kolterman OG, Kim DD, Shen L, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health-Syst Pharm*. 2005;62:173-181.
 47. Kolterman OG, Buse JB, Fineman MS, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab*. 2003;88:3082-3089.
 48. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28:1092-1100.
 49. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27:2628-2635.
 50. Data on file, Amylin Pharmaceuticals, Inc.
 51. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143:559-569.
 52. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005;28:1083-1091.
 53. Byetta [package insert]. San Diego, Calif: Amylin Pharmaceuticals, Inc.; 2006.

Managed Markets Commentary

Jeremy Gleeson, MD, FACP, CDE, Chief Quality Officer, Associate Medical Director, Chair, Division of Endocrinology, Lovelace Sandia Health Systems

Despite the frequent lack of recognizable symptoms, long-term maintenance of glycemic control in patients with type 2 diabetes is necessary to prevent complications over time. There are many barriers to effectively treating type 2 diabetes and maintaining long-term glycemic control. In addition to adjusting to an often complex medication regimen, effective diabetes management also requires complex behavioral changes for many patients.

In my clinical experience, lack of education is rarely the major reason for nonadherence and, as a result, failure to meet glycemic goals. Most importantly, the patient must share the clinician's objective to achieve blood glucose control goals. This alignment is of critical importance. Choosing the "wrong" drug is not usually one of the main reasons for failure to reach glycemic goal; the pharmacologic agents for diabetes (excluding insulin) are all of approximately equal efficacy. Failure to increase drug dose to the maximum is likewise not a dominant reason for inadequate glycemic control, as titrating any drug to maximal dose has a very modest incremental effect.

Failure to meet glycemic goals is greatly impacted by the clinician's willingness to alter treatment strategies in order to obtain the greatest benefit for the individual patient. In the experience of many clinicians, the failure to add additional drugs to implement combination therapy is the major reason for failure to reach goal.

Additional reasons patients fail to meet goals and/or comply with pharmacologic treatment are the complexity and costs of drug therapy and the occurrence of side effects. While side effects can usually be managed by a change in drug or dose, clinicians have less influence on issues related to the cost of treatment. In order to successfully treat type 2 diabetes, clinicians must address all of the factors that affect compliance.

IMPLEMENTING ADVANCES IN CARE

Combination Therapy. Because of the limited efficacy of available individual drugs, many patients require multiple drugs in combination. In order to achieve the best level of glycemic control, clinicians will often need to select drugs from different classes with complementary mechanisms of action. Clinicians are increasingly accepting combination therapy as the standard of type 2 diabetes care. While a higher number of patients are now being treated with combinations compared to several years ago, this change is occurring at a much slower than ideal pace.

Greater efficacy, with fewer side effects, may be achieved by using several drugs in less than maximal doses, rather than a single drug at maximal dose. In some cases, the newer sin-

gle-pill combination medications offer a way to achieve this goal while minimizing the cost and complexity of the treatment regimen.

It is well known that patients with type 2 diabetes who are using older drugs such as metformin and sulfonylureas may have a progressive deterioration in control despite consistent drug therapy. This phenomenon occurs as a result of progressive beta-cell dysfunction, rather than true drug failure. Some of the newer agents may slow, or even reverse, beta-cell dysfunction and thereby prevent progressive deterioration in control.

Newer agents, such as incretin mimetics and the investigational incretin enhancers, may also have other benefits. While practicing clinicians are beginning to accept these incretin mimetics into their prescribing practices, it remains to be seen in clinical trials if the need for injections will be a barrier to use. Inhaled insulin, equal in efficacy to injectable, premeal, rapid-acting insulin analogues, offers a novel route of insulin delivery that may be more acceptable to some patients.

IMPACT OF MANAGED CARE FORMULARIES

Managed care organizations can facilitate pharmacologic management of type 2 diabetes by providing physicians with a broad-based diabetes formulary. This represents a challenge, however, since additional drugs will inevitably result in increased drug costs, while the cost savings from improved control will generally not accrue for many years. Requiring use of older, less costly drugs, such as metformin, first in appropriate patients is not unreasonable. However, newer and more expensive drugs should be available for subsequent use in combination regimens. As always, decisions about formulary placement represent a balance among efficacy, safety, and cost.

Exenatide is an example in our organization of a newer, more expensive drug that can only be used after a patient has failed to reach treatment goals with metformin or a sulfonylurea (consistent with Food and Drug Administration labeling). Exenatide is then available at a "preferred brand" (tier 2) copayment. Inhaled insulin does provide an added benefit in its mode of administration for those patients with compliance issues related to subcutaneous medications. Nonetheless, it has not been shown to offer an efficacy benefit over insulin injections, and also has additional safety concerns and contraindications related to pulmonary disease. Given these issues, the additional costs associated with inhaled insulin may well result in restrictive formulary placement. Placing drugs such as these on high tiers with very high copayments will unfortunately inevitably limit access for many patients, making attainment of treatment goals more difficult. n

To be eligible for documentation of credit, participants must read all monograph content (print or online), go to www.princetoncme.com to complete the 10-question post-test with a score of 70% or better, and complete the online evaluation form.

Get your documentation of credit **NOW**

Completing a post-test at
www.princetoncme.com
is as easy as **1-2-3...**

1

Go to the "Post-Tests" page and click on the title of this activity.

2

Fill out the fields under "New Users Register"
("Existing Users" log in with e-mail address and password).

3

Successfully complete the post-test and evaluation form and gain access to your printable documentation of credit.

LIVE step-by-step assistance is available Monday – Friday 8:30 am - 4:30 pm ET at 609-371-1137
OR e-mail info@princetoncme.com.

To be eligible for documentation of credit, participants must read all monograph content, complete the 10-question post-test with a score of 70% or better, and complete the evaluation form. Please e-mail info@princetoncme.com or call 609-371-1137 if you have questions or need additional information.

[CLICK HERE TO TAKE POST-TEST ONLINE](#)

PUBLISHING STAFF

Senior Vice President,
Editorial Operations
Rosemary Hodgson

Vice President,
Educational Services
Randy P. Robbin

Director, Educational Services
Mary Johnson

Senior Program Director
Erin E. Phelps

Program Director
Genie M. Go

Associate Program Director
Kristin Dickie

Assistant Program Director
Jennifer Manahan

Medical Editor
Anastasia Perkowski

Program Coordinator
Kristen Jassin

Assistant Program Coordinator
Carol Matyas

Office Manager
Joan Heary

Administrative Assistant
Tom Fochetta

Production Manager
Bradley R. McGinnis

National Accounts Manager
Mike T. Kearney

Senior National Accounts Manager
Michael DiBella

Grant Development
Rich Keenan
Greg Paladino

Senior Vice President,
Publisher
Chris Ciraulo

President/CEO
Jeff Hennessy

First Report® is a registered trademark of Princeton Media Associates, LLC, 300 Rike Drive, Suite A, Englishtown, NJ 07726. (609) 371-1137. www.princetoncme.com. Copyright ©2006 by Princeton Media Associates, LLC. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, without first obtaining permission from the publisher. Postmaster: Send address changes to: Princeton Media Associates, 300 Rike Drive, Suite A, Englishtown, NJ 07726. E-mail can be sent to info@princetoncme.com.



Publisher's Note: The opinions expressed in this publication are those of the authors, presenters, and/or commentators and are not attributable to the sponsor or the publisher or editor of *First Report*®. Clinical judgment must guide each professional in weighing the benefits of treatment against the risk of toxicity. Dosages, indications, and methods of use for products referred to in this publication are not necessarily the same as indicated in the package insert and may be derived from the professional literature or other clinical courses. Consult complete prescribing information before administering.