New Concepts in Diabetes: How Multihormonal Regulation Can Improve Glycemic Control

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He has received numerous awards, including the Peel Medical Research Award, Mason Medical Research Foundation Award, Newcastle Research and Scientific Committee Research Award, and Southern Section AFCR Young Faculty Award. In 2000, Davis was both nationally and internationally recognized as the recipient of the Novartis Award for Diabetes Research. His current research includes studies of hypoglycemic counter-regulatory dysfunction, exercise physiology, autonomic nervous system control of metabolism, and new therapies for type 1 and type 2 diabetes.

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Ratner received his medical degree from Baylor College of Medicine, Houston, Texas, where he also completed his internal medicine training, and completed fellowship training in endocrinology and metabolism at Harvard Medical School and the Joslin Diabetes Center in Boston.

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1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.

2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.

3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.

4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

5. Seek and publish content that does not duplicate content in the Journal of Managed Care Pharmacy.

6. Subject all supplements to expert peer review.
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S9  Continuing Education*:
    Record of Completion, Posttest, and Program Evaluation

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. explain the rationale behind the development of new multihormonal therapies for
   the treatment of type 1 and type 2 diabetes,
2. list how these therapies differ from insulin and oral agents as well as the mechanism
   whereby these treatments may help improve plasma glucose levels in patients with
   type 1 and type 2 diabetes,
3. describe the clinical opportunities and challenges presented by these novel gluco-
   regulatory therapies, and
4. discuss the impact of these new treatments in the managed care arena.

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* A total of .10 CEU (1.0 contact hour) will be awarded for successful completion of this continuing
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New Concepts in Diabetes: How Multihormonal Regulation Can Improve Glycemic Control

LAWRENCE BLONDE, MD, FACP; DANIAL E. BAKER, PharmD, FASHP, FASCP; STEPHEN N. DAVIS, MD, FRCP; and ROBERT E. RATNER, MD

ABSTRACT

SUMMARY: It is estimated that 18.2 million Americans are currently living with diabetes, a disease that continues to place significant economic burdens on patients, their families, health plans, systems, and society. Recent data from the American Diabetes Association indicates that the annual direct and indirect costs of diabetes are rapidly increasing. Improved glycemic control—which has been repeatedly demonstrated to reduce the risk of developing microvascular complications and is likely to reduce the risk of macrovascular complications associated with type 1 and type 2 diabetes—has the potential to improve quality of life and reduce health care expenditures. However, despite recent advances in oral anti-diabetic agents and insulin management (e.g., development of rapid- and long-acting insulin analogs and continuous subcutaneous insulin infusion [CSI]), only a portion of the patient population is able to achieve the goals for glycemic control recommended by the American Diabetes Association, the American College of Endocrinology, and other guideline-setting organizations. Moreover, improved glycemia achieved with present therapeutic modalities may be associated with the risk of hypoglycemic events and undesired weight gain. The latter can negatively affect plasma lipids, blood pressure, and therapy adherence.

New research into the pathophysiology of diabetes indicates that multiple hormones—not just insulin and glucagon but amylin, GLP-1 (a glucagon-like peptide), and others—are involved in the regulation of plasma glucose levels, providing insight into why even insulin is often ineffective in helping patients with diabetes achieve their glycemic goals. The use of analogs of these newly recognized, important glucoregulatory hormones; agents that delay the degradation of the hormones and therefore raise their concentration; and/or agents that bind to their receptors may facilitate achievement of improved glycemia. One of these agents, pramlintide, represents the first new potential antihyperglycemic agent for the treatment of type 1 diabetes since insulin was introduced more than 80 years ago.

There is substantial potential for these agents to improve glycemic control and patient outcomes and to reduce the personal, societal, and economic burdens of diabetes. Some of these novel multihormonal glucoregulatory therapies will likely soon become important components of the diabetes armamentarium. It is therefore important that managed care pharmacy decision makers learn about them.

KEYWORDS: Diabetes, Cost, Multihormonal glucoregulatory therapy, Managed care

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Diabetes is increasing at epidemic proportions. According to diabetes statistics from 2002 published by the National Institutes of Health (NIH), 6.3% of the total U.S. population has diabetes (18.2 million people). There are about 1.3 million new cases diagnosed each year. A recent article in the Journal of the American Medical Association estimates that the lifetime risk of diabetes for a male born in the year 2000 in the United States is 32.8%. The lifetime risk increases to 38.5% for a female born in the year 2000. If the individual is Hispanic, the lifetime risk of diabetes increases to 45.4% for males and 52.5% for females.

In 2002, direct and indirect costs in the United States attributable to diabetes totaled $132 billion. Direct medical expenditures had doubled just since 1997 to $91.8 billion, while indirect expenditures from lost workdays, restricted activity days, mortality, and permanent disability due to diabetes totaled $39.8 billion. Many of these costs were incurred by individuals below the age of 65 years, so this is not just a Medicare problem. Employers, health plans, and private and public organizations need to actively mobilize resources and strategies to deal with this emerging diabetes epidemic.

Acute and especially chronic micro- and macrovascular complications of diabetes significantly impact the health and quality of life of patients and the cost of their care. Diabetes is the leading cause of blindness in adults. It is responsible for a 2- to 4-fold increase in cardiovascular disease, and is the leading cause of end-stage renal disease in patients in the United States. It causes a 15-fold increase in the risk of lower-extremity amputations.

These statistics point to the need to prevent diabetes through improved risk assessment, education, and implementation of lifestyle changes, especially in those found to have prediabetes. Patients with diabetes need to be effectively risk-stratified and have early and more effective interventions to treat hyperglycemia as well as the often accompanying hypertension and dyslipidemia.

Studies such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that reduction of glycemia as measured by A1C can significantly reduce the development and progression of the complications of diabetes. In the DCCT, a reduction of A1C from 9.1% to 7.2% lowered the incidence of retinopathy by 63%, and nephropathy by 54%. In the UKPDS, a reduction of glycated hemoglobin (A1C) from 7.9% to 7% was associated with a 21% decreased risk of retinopathy and a 34% decreased risk of nephropathy. The American Diabetes Association recommends a goal of less than 7%. The American Association of Clinical Endocrinologists recommends a target of <6.5%. With 40% to 50% of all patients having an A1C
greater than 8%, there is an unmet need to achieve appropriate glycemic control.

Several pharmacologic agents are presently used to treat the hyperglycemia of diabetes. Insulin is required in all type 1 diabetes patients. Many oral antidiabetic agents are available for the treatment of type 2 diabetes patients, including the biguanide metformin, sulfonylureas, nonsulfonylurea secretagogues, alpha glucosidase inhibitors, and the thiazolidinediones. While all of these agents can improve glycemia, monotherapy is not likely to maintain control over a long period of time. Combinations of agents with complementary mechanisms of action may be required in many patients in order to address the insulin resistance and relative insulin deficiency present in all patients with type 2 diabetes.

Most type 2 diabetes patients have insulin resistance that begins years before diabetes is diagnosed and persists throughout the course of the disease. At diagnosis, there is at least a relative insulin deficiency and, over time, there is a continual decline in beta cell insulin secretion. The UKPDS demonstrated continual deterioration of beta cell function associated with type 2 diabetes despite drug therapy, diet, or exercise.

Even with the use of multiple daily injections of short- and long-acting insulins in type 1 patients and combinations of the presently available antihyperglycemic agents, including insulin in type 2 diabetes patients, there remain many challenges to optimal diabetes care including the following:

- Failure of many patients to attain and sustain good long-term glycemic control
- Difficulty balancing reduction in hyperglycemia with the risk of hypoglycemia
- Inadequate postprandial glucose control, even in some patients with A1C levels that achieve present targets
- Unpredictable glucose fluctuations
- Weight gain associated with many therapies, which can then increase blood pressure, triglycerides, and total cholesterol

There are several approaches to addressing the unmet needs in diabetes control. Improving patient adherence to medical nutrition therapy and appropriately prescribed exercise as well as pharmacologic therapies will continue to be essential. Physicians and their patients may consider progressing earlier to combination therapy including the addition of insulin in type 2 diabetes patients.

## Components of Glycemic Control

Suboptimal glycemic control is characterized by excessive postprandial hyperglycemia as well as a wide variation in glucose levels throughout the day. As discussed, there are risks of hypoglycemia and weight gain that increase in direct proportion to improvements in glycemic control through increased insulin use. These limitations may occur, in part, because present therapies fail to correct other hormonal abnormalities in diabetes subjects, including inappropriate glucagon levels and an absolute or relative deficiency of the recently identified hormone amylin. Therapy that addresses these multihormonal abnormalities may provide an important approach to improving glycemic control.

In a nondiabetic individual, blood glucose levels increase only modestly after meals but return to baseline within 2 hours. Several mechanisms combine to control nondiabetic postprandial glycemia. Endogenous hepatic glucose production is inhibited both by appropriately timed insulin release and a decrease in glucagon levels. Endogenous insulin produced by the pancreas also facilitates meal-derived glucose uptake primarily in muscle. In patients with diabetes, postprandial hyperglycemia occurs because of relative or absolute insulin deficiency, failure to suppress postprandial glucagons and endogenous glucose production, and a failure to synchronize gastric emptying and insulin release.

The role of glucagon in normal physiology and its contribution to the pathophysiology has been well recognized. In the 1960s and 1970s, diabetes was described as a bihormonal disease characterized by decreased insulin and increased glucagon. In nondiabetic individuals, glucagon is suppressed postprandially so that the signal to the liver to produce glucose will decrease as described above. In diabetic subjects, postprandial glucagon is not suppressed and may actually be paradoxically elevated. The resultant failure to inhibit endogenous hepatic glucose production contributes significantly to postprandial hyperglycemia.

Gastric emptying also plays an important physiological role in postprandial glucose regulation. As plasma glucose levels increase, gastric emptying is normally restrained. In contrast, when glucose levels are low and especially in the case of hypoglycemia, gastric emptying is accelerated.

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**FIGURE 1** Physiologic Actions of Amylin on Reducing Appetite, Lowering Glucagon Levels, and Slowing Gastric Emptying

Model of Multihormonal Regulation of Glucose Homeostasis

- **Brain**
  - **Food Intake**
  - **Gastric Emptying**
  - **Stomach**
  - **Liver**
  - **Postprandial Glucagon**
  - **Amylin**
  - **Insulin**
  - **Glucose Disposal**
  - **Rate of glucose disappearance**
  - **Rate of glucose appearance**

*Model derived from animal studies. *Inferred satiety effect.*
emptying is accelerated so that food from the stomach can rapidly enter the circulation via the small bowel.

II Role of Hormones

Along with insulin, pancreatic beta cells cosecrete amylin, a hormone first identified in 1987. Amylin is colocated, and cosecreted with pancreatic beta cell insulin and has a neuro-endocrine mode of action.\textsuperscript{11} It regulates the rate of gastric emptying, suppresses postprandial release of glucagons, and contributes to the satiety signal in animals and possibly in humans.\textsuperscript{11} A model of multihormonal regulation to achieve glucose homeostasis is shown in Figure 1.

Amylin is absolutely or relatively deficient in patients with diabetes.\textsuperscript{11,12} Patients with type 1 diabetes and beta-cell destruction have both absolute insulin deficiency and low or undetectable concentrations of amylin. In the type 1 diabetes patient, auto regulation of gastric emptying is impaired because amylin is markedly deficient. In insulin-treated type 2 diabetes patients with beta-cell dysfunction and relative insulin deficiency, measurable amylin may be noted in the fasting state, but there is a decreased postprandial response. Thus, absolute amylin deficiency occurs in type 1 diabetes, and relative deficiency occurs with significantly truncated levels of amylin in type 2 diabetes. Amylin-deficient laboratory animals gain significantly more weight, have accelerated gastric emptying, and an increase in postprandial release of glucagon.\textsuperscript{14}

Human amylin can aggregate, form insoluble particles, and adhere to surfaces, making it unsuitable for pharmacologic use. Pramlintide acetate is a synthetic amylin analog specifically engineered to address these issues while at the same time retaining the ability to bind to amylin receptors with a similar or greater potency than human amylin. Three amino acid substitutions introduced in pramlintide decrease the self-adhesive properties of this molecule while maintaining its bioeffectiveness. For example, pramlintide has been shown to be very potent in restraining glucagon.\textsuperscript{11}

Pramlintide therapy in type 1 diabetes patients modulates nutrient delivery from the stomach to the small intestine. Pramlintide also restrains hepatic glucose production by suppressing postprandial glucagon secretion. Since pramlintide is a peptide, oral administration is not effective. It must be administered by an alternate route—currently by subcutaneous injection.

II Review of Evidence

Two pivotal phase III registration trials studied pramlintide administered for 52 consecutive weeks to type 1 and type 2 diabetes patients who were being treated with insulin.\textsuperscript{11,12} A stable insulin cohort analysis was prospectively defined as those subjects who did not change their total daily insulin dose (± 10%) during the study. This better isolated the independent effect of pramlintide. The placebo and pramlintide treatment groups in these trials were well balanced in terms of sex, race, age, weight, body mass index, A1C, and duration of diabetes. Figure 2 demonstrates the mean change in A1C for the stable insulin cohort in both the type 1 and type 2 diabetes pivotal phase III studies. In the type 1 study, the mean change from baseline to week 52 was -0.7% and 0.1% for the pramlintide and placebo groups, respectively. In the type 2 study, the mean change from baseline to week 52 was -0.6% and 0.1% for the pramlintide and placebo groups, respectively.\textsuperscript{11,12}

Treatment with insulin in type 1 patients and with insulin secretagogues and/or insulin in type 2 diabetes patients is frequently associated with weight gain.\textsuperscript{12} In contrast, in both the pramlintide type 1 and type 2 studies, the pramlintide plus insulin treatment group had a reduction in body weight.

Approximately 5,000 patients have been exposed to pramlintide in studies worldwide, and about 265 patients have had an exposure of 2 years or longer. To date, there is no evidence of
cardiac, hepatic, or renal toxicity. There have been no clinically significant changes in vital signs, lipid levels, ECG, or non-glucose laboratory parameters. Pramlintide has been associated with gastrointestinal side effects consisting of a spectrum from fullness to nausea. In clinical trials, there was a doubling in nausea compared with placebo. Nausea is an early phenomenon mostly seen in type 1 patients. It is generally mild to moderate in intensity and usually diminishes or abates with continued use. Slowly titrating from a starting dose of 15 µg to the final dose will diminish the incidence of nausea.

Pramlintide has not been shown to cause hypoglycemia or inhibit normal counter regulatory responses to hypoglycemia since hypoglycemia overrides pramlintide effects on gastric emptying and glucagon suppression. However, in the long-term pramlintide studies, there was an increased incidence of hypoglycemia in the pramlintide-treated patients; this was particularly notable in the studies involving type 1 diabetes patients but less so in the studies involving type 2 diabetes patients. Hypoglycemia tended to occur early in these pramlintide studies, usually during the first 4 weeks. The studies were conducted without active adjustment of concomitant insulin dosing, which likely contributed to this phenomenon, and pramlintide-induced nausea in some patients was a likely additional contributor to the risk of hypoglycemia.

**Effects of Pramlintide Dose Titration**

A dose titration study of pramlintide was performed to examine whether the early risk of hypoglycemia could be ameliorated by active adjustment of concomitant insulin dosing and up-titration of pramlintide to mitigate potential nausea. The study was conducted in 2 periods; a 4-week pramlintide (or placebo) dose initiation period and a 23-week insulin dose optimization period.

The study was designed to achieve noninferiority for the A1C effects obtained in the pramlintide- and placebo-treated type 1 diabetes patients already established on an intensive regimen of either subcutaneous insulin pump therapy or multiple daily injections of insulin. In both treatment groups, subjects were instructed to adjust insulin therapy in order to achieve predetermined fasting, premeal, and postprandial glucose concentrations.

During the 4-week pramlintide dose initiation period, subjects progressively titrated their pramlintide through doses of 15 to 30, 45, and 60 µg to a maintenance dose of 30 or 60 µg thrice daily, based on tolerability relative to gastrointestinal side effects. During initiation of pramlintide (or placebo), a 30% to 50% reduction in short-acting preprandial insulin dose was recommended because pramlintide treatment decreases gastric emptying and may be associated with the ingestion of less food at meals, due to earlier satiety and/or the occurrence of nausea. During the 23-week insulin dose optimization period, the pramlintide dose achieved during the initiation period was continued and insulin therapy was optimized, targeting a preprandial blood glucose concentration between 110 and 140 mg/dL and a postprandial blood glucose concentration between 140 and 180 mg/dL. A1Cs fell from about 8.2% to about 7.5% in both treatment groups.

The study was successful in that the titration strategy succeeded in decreasing the incidence of nausea, and the prospective reduction in preprandial insulin dose decreased the early incidence of significant hypoglycemia while enabling patients to then intensify their treatment regimen in the optimization phase to lower A1C by study end.

In summary, in patients with type 1 diabetes who are initiating pramlintide therapy, the dose should be gradually titrated up to the final dosage in order to reduce the occurrence of significant nausea. For type 2 diabetes patients, pramlintide dose titration at initiation is generally not necessary because significant nausea is a less frequent problem than in type 1 patients. One can begin with a 120 µg dose and, if nausea occurs, the dose can be decreased.

In both type 1 and type 2 diabetes patients who are initiating pramlintide, self-monitoring of blood glucose is critical, and proactive preprandial insulin reduction of 30% to 50% is important in order to decrease the risk of hypoglycemia. It may also be necessary to modify the insulin-to-carbohydrate ratio in those subjects who are performing carbohydrate counting. A number of other insulin modification strategies may be required in order to optimize glycemic control in patients treated with pramlintide and insulin. Pramlintide should not be taken if a meal is omitted. Otherwise, the dose of pramlintide will be constant regardless of the blood glucose level, food composition and quantity, and physical activity.

Studies have demonstrated that pramlintide therapy is associated with
- decreases in postprandial hyperglycemia,
- reduced glucose fluctuations,
- improved A1C levels, and
- decreased weight gain or even weight loss in spite of improved glycemia.

**Effects of Exenatide**

GLP-1, a glucagon-like peptide, also plays an important role in the regulation of postprandial glycemia. GLP-1 is a hormone that is released from the L-cells predominantly in the ileum and colon. In humans, GLP-1 functions include
- decreased food intake through action on the hypothalamus,
- enhanced glucose-dependent insulin secretion, and
- suppression of postprandial glucagon secretion.

GLP-1 is deficient in patients with type 2 diabetes. Increasing GLP-1 decreases glycemia. However, native GLP-1 has a very short half-life of approximately 2 minutes in the circulation, which means that pharmacologic treatment with GLP-1 would require continuous infusion. Exendin-4, or exenatide, is derived from the salivary secretions of the Heloderma suspectum, also known as the Gila monster, a lizard found in the Southwest United States.
Exendin-4 is believed to have a possible endocrine function in the Gila monster modulating appetite and metabolism. Exenatide binds to human GLP-1 receptors and exhibits GLP-1-like activity. However, it has a much longer half-life than GLP-1, allowing it to be administered subcutaneously twice a day. An extended-release form of exenatide is also under investigation.

The available data on exenatide are based on phase II trials; phase III data was also recently presented in abstract form at a scientific meeting. Exenatide has been shown to lower fasting and postprandial glucose concentrations by a number of mechanisms:

- Stimulation of insulin secretion in a glucose-dependent fashion; in other words, exenatide stimulates the secretion of insulin only in the presence of elevated circulating glucose concentrations, thus minimizing the risk of hypoglycemia
- Suppression of postprandial glucagon secretion which, as noted above, is often inappropriately elevated in patients with diabetes
- Slowing and synchronizing gastric emptying and, therefore, nutrient delivery with insulin availability

In a phase II clinical study, the effect of exenatide was assessed in type 2 diabetes patients who were receiving metformin and/or sulfonylurea treatments. A single dose of exenatide, 0.08 µg/kg, was administered subcutaneously either twice daily at breakfast and dinner, twice daily at breakfast and bedtime, or thrice daily at breakfast, dinner, and bedtime. Placebo was administered subcutaneously thrice daily. The 3 exenatide treatment arms yielded similar results. On day 28, postprandial and fasting glucose concentrations were significantly lower in exenatide-treated groups. There was also a significant reduction of 1% in A1C in the exenatide-treated group in just 28 days.16

Side effects of exenatide are primarily gastrointestinal. Increased nausea was generally transient and dissipated over time. Exenatide is a promising therapeutic for patients with type 2 diabetes.

In a phase III study, exenatide was administered for 30 weeks to 336 people with type 2 diabetes inadequately controlled with at least 1,500 mg of metformin. There were 3 arms based on dose of exenatide—5 µg, 5 µg titrated up to 10 µg, or placebo—all given subcutaneously twice daily. In the higher-dose group, there was an average drop in A1C of 0.8% and an average decrease in weight of 6.2 pounds. The most common side effect was nausea, which was described as mild to moderate. Hypoglycemia was no more frequent in the treatment group than in the placebo group.17 In a second phase III study, 773 people on both metformin and sulfonylurea were treated with exenatide or placebo. In this study, the 10-µg group had a mean reduction in A1C over placebo of 1%. Mild to moderate hypoglycemia occurred in 27.8% of those receiving 10 µg of exenatide, 19.2% of those receiving the 5 µg dose, and 12.6% of those receiving placebo.18

Another possible future therapeutic agent is an oral inhibitor of the DPP-IV (dipeptidyl peptidase IV) enzyme which would, in turn, slow GLP-1 inactivation. Native GLP-1 has a short duration of effect due to degradation by DPP-IV, so an orally active DPP-IV inhibitor could potentiate GLP-1 levels and thus improve the postprandial glycemic response. Studies with such agents are currently being conducted.

### Application to Managed Care

Novel multihormonal therapy offers significant potential to improve the care of patients with diabetes. Postprandial hyperglycemia involves dysfunction of multiple hormones, and many patients may need such therapeutic advances added to treatment with presently available antidiabetic agents in order to achieve optimal glycemic control.

However, many patients fail to attain the glycemic control that is available with today’s therapy. Much of this failure is the lack of organized systems of diabetes care delivery. The Institute of Medicine’s 2001 report, Crossing the Quality Chasm: A New Health System for the 21st Century noted:

> The healthcare system is poorly designed. Even for the most common conditions like diabetes and cancer, there are few programs that use multidisciplinary teams to provide comprehensive services for patients.

In the past few years, a number of employer groups and health care systems throughout the United States have developed diabetes disease management programs to better organize their diabetes care delivery, improve both processes and outcomes of care, and lower the escalating costs of diabetes. Most management programs apply the following interventions:

- A registry of patients with diabetes is created utilizing pharmacy data, hospital and outpatient visit diagnoses, and laboratory data
- Patients in the registry are risk-stratified
- Risk-specific interventions are applied
- Outcomes are regularly evaluated and the results are used to update care plans as needed

Such systematic approaches have been demonstrated to improve processes and outcomes of care. Twelve-month data on 193 patients in a diabetes disease management model demonstrated that the number of patients achieving an A1C of less than 7% increased by more than 50%, and more than 97% of the patients with an A1C of greater than 8% had a change made to their treatment regimen.19

The National Diabetes Education Program (NDEP), a joint venture of the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK) and the Centers for Disease Control and Prevention (CDC), recently launched a Web site—www.betterdiabetes.nih.gov—to help users implement better systems with which to deliver improved diabetes care. Another Web site—www.diabetesatwork.org—hosted by the Washington Business Group on Health provides employers, employees, health plans, consumers, and others with support information about the impact of diabetes in the workplace. Increasing knowledge about diabetes mellitus and benefits of its treatment and structuring better systems for delivering diabetes care will help reduce the gap between current and desired diabetes processes and outcomes.

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New Concepts in Diabetes: How Multihormonal Regulation Can Improve Glycemic Control

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## Conclusion

Blood glucose levels, particularly postprandial glycemic levels, are regulated by the complex interplay of insulin, glucagon, amylin, GLP-1, and other hormonal and neural stimuli. Current therapy focuses on augmenting the availability and/or activity of insulin, which is important, but often insufficient to control postprandial hyperglycemia; avoid wide fluctuations in blood glucose; and achieve optimal glycomic control in patients with both type 1 and type 2 diabetes. Present therapy is also often associated with an increased risk of hypoglycemia and weight gain, which represent major barriers to optimal glycomic control.

Clinical trials with pramlintide have demonstrated improved A1C values, reduction in postprandial glucose excursions, and absence of weight gain or decreased weight, particularly in overweight patients. Improved glycomic control was also achieved without an overall increased risk for hypoglycemia or even a possible reduction in risk postinitiation. Thus, pramlintide appears to be able to address some unmet treatment needs.

Treatment with exenatide in patients with type 2 diabetes not controlled by metformin and/or sulfonylureas may also be able to address some unmet needs through glucagon-dependent stimulation of insulin secretion, suppression of postprandial glucagon secretion, and coordination of insulin secretion and the rate of nutrient delivery to the small intestine. Studies show that exenatide lowers fasting and postprandial glycosmia and is associated with reduced or absent weight gain or even weight loss.

## DISCLOSURES

This article is based, in part, on the proceedings of a symposium held on October 16, 2003, at the Academy of Managed Care Pharmacy’s 2003 Educational Conference in Montreal, Quebec, Canada, and supported by an unrestricted educational grant from Amylin Pharmaceuticals, Inc. The symposium was moderated by Debra J. Stern, RPh, vice president, Reperts, Inc., Irvine, California. Stern discloses that she is a consultant to Amylin, Serono, Genetech, and Amgen pharmaceutical companies.

The authors received an honorarium from Amylin Pharmaceuticals, Inc., for participation in the symposium and preparation of this program. Author Lawrence Blonde discloses that he has consulted for Lifescan and Merck/Schering-Plough, has received grant/research support and has consulted for Amylin, Aventis, BD, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly and Company, EMD, Merck & Co., Inc., Novo-Nordisk, Novartis, Pfizer, and Sanofi-Aventis, and has received honoraria from Takeda and Wyeth; author Daniel E. Baker discloses that he has consulted for Amylin; author Stephen N. Davis discloses that he has received grant/research support from Aventis and has consulted for Amylin; and author Robert E. Ratner discloses that he has received grant/research support from Amylin, GlaxoSmithKline, Pfizer, GMP Endo Therapeutics, Takeda, Aventis, and Novo Nordisk pharmaceutical companies and has consulted for Amylin, Takeda, Aventis, and Novo Nordisk.

Blonde served as principal author of the study. Study concept and design were contributed primarily by Ratner. Analysis and interpretation of data were contributed by Baker and Davis. Drafting of the manuscript and its critical revision was the work of all authors. Statistical expertise was contributed by Stern, and administrative, technical, and/or material support was provided by Kathleen Moreo, president, Professional Resources In Management Education, Inc. (PRIME).

## DISCLOSURES

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## ACKNOWLEDGMENT

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## REFERENCES

21. Stern, administrative, technical, and/or material support was provided by Kathleen Moreo, president, Professional Resources In Management Education, Inc. (PRIME).
Continuing Education

New Concepts in Diabetes:
How Multihormonal Regulation Can Improve Glycemic Control

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**1.** In 2002, the direct and indirect costs of diabetes in the United States amounted to
   a. $98 billion.
   b. $132 million.
   c. $132 billion.
   d. $98 million.

**2.** The main cause of microvascular complications of diabetes is
   a. compliance to a diabetic diet.
   b. economic status.
   c. unsatisfactory glycemic control.
   d. ineffective medical care.

**3.** Complications of diabetes cause significant impact on
   a. the health of the patient.
   b. quality of life of the patient and family.
   c. cost of care.
   d. All of the above

**4.** Due to the rising cost of diabetes, employers, health plans, and private and public organizations are recognizing the need to address all of the following except
   a. preventing diabetes through risk assessment and consumer education.
   b. placing a limit on the number of patients with diabetes that a managed care organization must cover.
   c. effectively risk-stratifying those with diabetes for early and more effective interventions.
   d. controlling the impact of diabetes through new advances that will improve glycemic control.

**5.** Essential components of improving glycemic control entail all of the following except
   a. improving patient behaviors.
   b. motivating patients to exercise.
   c. understating diet restrictions.
   d. limiting benefits to patients who do not adhere to their prescribed treatment.

**6.** Studies have demonstrated that pramlintide therapy is associated with
   a. increases in postprandial hyperglycemia.
   b. increased glucose fluctuations.
   c. higher A1C levels.
   d. decreased weight gain or even weight loss in spite of improved glycemia.

**7.** A pancreatic beta cell hormone known as amylin does all of the following in animals and/or humans except
   a. regulate the rate of gastric emptying.
   b. increase the secretion of insulin.
   c. suppress postprandial release of glucagons.
   d. contribute to the satiety signal.

**8.** A therapeutic goal of pramlintide in patients with type 1 diabetes is to
   a. modulate nutrient delivery from the stomach to the small intestine.
   b. increase gastric emptying.
   c. inhibit normal counter-regulatory responses to hypoglycemia.
   d. increase glucagon secretion.

**9.** The main side effect that has been identified in clinical trials of pramlintide is
   a. diarrhea.
   b. nausea.
   c. heartburn.
   d. chest pain.

**10.** In order to reduce the cost and improve treatment of patients with diabetes, health care professionals should
   a. strive to implement a systematic approach to delivering diabetes care using a team of health care professionals.
   b. provide educational resources for patients and families to better understand and participate in the management of their disease.
   c. consider use of novel therapeutic approaches to improve glycemic control.
   d. All of the above

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Please indicate the correct answers on the Record of Completion.
New Concepts in Diabetes: How Multihormonal Regulation Can Improve Glycemic Control

Objective:
1. explain the rationale behind the development of new multihormonal therapies for the treatment of type 1 and type 2 diabetes,

2. list how these therapies differ from insulin and oral agents as well as the mechanism whereby these treatments may help improve plasma glucose levels in patients with type 1 and type 2 diabetes,

3. describe the clinical opportunities and challenges presented by these novel glucoregulatory therapies, and

4. discuss the impact of these new treatments in the managed care arena.

Using the scale above for questions 1-4, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Objective:
5. What is your overall rating of this program?

6. How would you rate the pertinence of this program material to your practice?

7. To what degree was there promotional bias? (check one)
   a. Not at all
   b. Somewhat
   c. A great deal

8. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
   1 = No change
   2 = Significant change

9. Please indicate the length of time it took to complete this program. (circle selection(s))
   Hours: 1 2 3
   Minutes: 0 15 30 45

10. Please rate the difficulty factor for completing this CE program. (circle selection)
    Easy  Moderate  Difficult

11. Please rate your willingness to recommend this program to colleagues (circle selection)
    Very willing  Willing  Not willing

12. Please indicate which venue you prefer for obtaining continuing education. (circle selection)
    Written monograph  Slides  Videos  Internet-based

I would like more information on this topic as it becomes available.
Yes _____  No _____

Recommendations for future programs: ________________________

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Comments: ________________________

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