ABSTRACT

The incidence of diabetes is projected to double over the next 25 years, resulting in staggering implications for international healthcare systems. Although current therapeutic strategies can be highly efficacious when appropriately instituted, there is a great need for refined tools that would help to preserve pancreatic function and facilitate physiologic insulin release or mimic its action more closely. A series of novel approaches have emerged in the last 12 months, many of which were recently presented at the American Diabetes Association 65th Scientific Sessions. This article will review the most recent clinical data regarding incretin mimetics, pramlintide, protein kinase C inhibitors, heparinoids, glitazars, inhaled insulin, insulin detemir, and islet cell transplantation. These agents have helped to further illuminate islet physiology, and clinical trials suggest that these novel drug classes may serve to supplement the clinicians' armamentarium in the future.


INCRETIN MIMETICS AND DPP-IV INHIBITORS

It has long been recognized that pancreatic beta cells secrete insulin in response to ambient glucose levels. Experiments have demonstrated that insulin is released in greater concentrations when glucose is administered orally as compared with infused intravenously. This realization led to the search for a hormonal system that signaled from the gastrointestinal tract to increase insulin release in what has been termed the “enteroinsular axis.” Ultimately, the incretin hormones were recognized. These hormones are released from the gastrointestinal tract in response to the ingestion of food and act on the pancreatic beta cells to enhance insulin secretion and reduce postprandial glucose excursions. Therefore, incretins create an important link between food ingestion and insulin release.

As 2 of the most predominant incretins, glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP) naturally represent potential therapeutic agents for the treatment of type 2 diabetes. These peptides augment the normal release of insulin in response to ambient glucose levels. However, exogenous GIP is comparatively less effective than GLP-1 at stimulating insulin secretion in persons with type 2 diabetes. As a result, drugs that can enhance the activity of GLP-1 have the greatest potential to contribute to the management of type 2 diabetes.

GLP-1 is released from intestinal L cells in response to the ingestion of food and under the influence of both neural and endocrine stimuli. The protein then circulates to the pancreas through the portal circulation where it has a number of effects. GLP-1 augments glucose-stimulated insulin secretion and suppresses glucagon secretion. Other effects include a reduction in the rate of gastric emptying and an anorexigenic effect to reduce food intake. Additional data suggest that...
GLP-1 also may enhance insulin-independent glucose disposal in the peripheral tissues. Provocative preclinical data have demonstrated that GLP-1 can increase beta-cell mass by stimulating beta-cell neogenesis and reducing beta-cell apoptosis.

GLP-1 is metabolized rapidly by the ubiquitous proteolytic enzyme dipeptidyl peptidase (DPP)-IV and has a half-life of less than 2 minutes before it is renally cleared. Consequently, 2 strategies have emerged to combat the reduced half-life of GLP-1. A series of long-acting, DPP-IV–resistant GLP-1 analogs have been developed for clinical use, including exenatide, liraglutide, CJC-1131, AVE010, and LY548806 (Table 1). These drugs bind to GLP-1 receptors with similar affinity and produce biological actions identical to those of native GLP-1, but they are resistant to DPP-IV–mediated inactivation and renal clearance. As a result, these compounds are able to exert more sustained GLP-1–like activity for longer periods of time in vivo.

An alternative therapeutic approach for prolonging the action of native GLP-1 is to inhibit the activity of the DPP-IV enzyme, thereby protecting endogenous GLP-1 from enzymatic destruction and prolonging its half-life. Several orally active agents that inhibit DPP-IV activity are being evaluated for the treatment of type 2 diabetes.

**EXENATIDE**

Exenatide is a synthetic version of exendin-4, a 39-amino acid peptide that was originally purified from the saliva of the Gila monster. It has been studied in a series of small clinical trials, and is the first GLP-1 analog to be approved by the US Food and Drug Administration (FDA) for use in patients with type 2 diabetes.

Exenatide is administered as a subcutaneous injection. Its manufacturers have released a pen device, similar to those available for insulin delivery, for easy self-administration. It is dosed twice a day at a dose of either 5 or 10 µg. Exenatide is renally cleared, but appears safe in patients with mild-to-moderate impairments in renal function; however, it is not recommended for patients with end-stage renal disease.

The efficacy of exenatide in glycemic control appears to be mild to moderate. An industry-funded trial randomized 733 subjects who were taking both metformin and a sulfonylurea to 5 or 10 µg of exenatide, or to placebo, twice daily in addition to their oral medications. Subjects were followed for 30 weeks. Those who entered the trial with a hemoglobin A1C (HbA1c) of less than 9% experienced a mean reduction in HbA1c of 0.5% at the higher dose, and of 0.4% at the lower dose of exenatide. Those who entered the study with an HbA1c of over 9% experienced mean improvements of 1.4% and 0.9% at higher and lower doses, respectively. After 6 months, subjects who received exenatide experienced progressive mild weight loss of 1.6 kg from baseline, which was significantly greater than the 0.9 kg lost by subjects in the placebo group.

Two earlier, smaller studies that also were funded by the manufacturer of exenatide examined the effect of exenatide in combination with either metformin or a sulfonylurea. Similar efficacy was noted in each of these studies (Table 2). Metformin did not increase the risk of hypoglycemia, and weight reductions were mild (approximately 1 kg) but progressive.

### Table 1. Incretin Mimetics and DPP-IV Inhibitors

<table>
<thead>
<tr>
<th>GLP-1 Analogs</th>
<th>DPP-IV Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Vildagliptin</td>
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<tr>
<td>CJC-1131</td>
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<tr>
<td>AVE010</td>
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<td>LY548806</td>
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DPP-IV = dipeptidyl peptidase-IV; GLP-1 = glucagon-like peptide-1.

### Table 2. Mean Changes in HbA1c in 2 Clinical Trials After 6 Months of Treatment with Exenatide

<table>
<thead>
<tr>
<th>Initial HbA1c</th>
<th>Exenatide + sulfonylurea</th>
<th>Exenatide + metformin + sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9%</td>
<td>-0.4</td>
<td>-0.4</td>
</tr>
<tr>
<td>&lt;9%</td>
<td>-0.7</td>
<td>-0.5</td>
</tr>
<tr>
<td>&gt;9%</td>
<td>-0.6</td>
<td>-0.9</td>
</tr>
<tr>
<td>&gt;9%</td>
<td>-1.2</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

Data from Kendall et al; Buse et al.

HbA1c = hemoglobin A1c.
Data presented at the American Diabetes Association 65th Scientific Sessions indicated that exenatide had similar efficacy to glargine insulin over 6 months, with both drugs achieving mean HbA1c reductions of 1%. Glargine resulted in lower fasting glucose, whereas exenatide resulted in lower postprandial glucose. Additionally, exenatide treatment resulted in significant weight loss (~2.3 kg) whereas glargine treatment resulted in weight gain (+1.8 kg). Furthermore, an 82-week, open-label, follow-up study that followed patients who were randomized to receive exenatide found a progressive weight loss of 4.5 kg and a sustained reduction in HbA1c.

The predominant side effects of subcutaneous exenatide are nausea and vomiting. These effects appear to be both dose dependent and common. In a 30-week, placebo-controlled study that compared 5 and 10 µg of exenatide, the incidence of nausea was 49% in subjects who took 10 µg twice a day, 39% in subjects who took 5 µg twice a day, and 21% in subjects on placebo. Vomiting was experienced by 14% of those on exenatide at either dose, compared with 4% of those on placebo. Diarrhea was experienced by 17%, 10%, and 7% of subjects who took the higher and lower doses of exenatide and placebo, respectively. These effects were severe enough to lead to study withdrawal by 5% of the participants. Similar side effects were noted in other studies. The degree of weight loss achieved appeared to be independent of whether or not nausea was reported. Hypoglycemia was generally mild or moderate, and predominantly occurred in patients who also received a sulfonylurea. There was no evidence of cardiovascular, pulmonary, hepatic, or renal toxicity, or of drug-related idiosyncratic side effects associated with exenatide.

LY548806

LY548806 is a GLP-1 analog that is resistant to rapid proteolysis by DPP-IV. Data presented in abstract form suggest intravenous treatment of hyperglycemia in acute care settings as a potential use for this agent. When given to 36 subjects with type 2 diabetes, LY548806 was metabolized quickly, with levels reaching a plateau within 30 to 60 minutes of infusion and becoming undetectable 1 hour subsequent to discontinuation of the infusion. At doses of greater than 10 µg per hour, LY548806 significantly and rapidly reduced fasting and prandial blood glucose levels. The drug was safe and appeared to be well tolerated, with no episodes of hypoglycemia; however, nausea was common.

CJC-1131

CJC-1131 is a DPP-IV–resistant GLP-1 analog. It forms an irreversible covalent bond with albumin following subcutaneous injection and, as a result, has a long half-life of approximately 10 days. A 12-week, randomized, controlled, multicenter study looked at the effects of a combination of CJC-1131 and metformin on glycemic control and body weight in 81 subjects with type 2 diabetes. The subjects had not achieved adequate glycemic control on metformin alone or on metformin plus a sulfonylurea, and were randomized to placebo, low-dose CJC-1131 (approximately 2.1 µg/kg daily), or high-dose CJC-1131 (approximately 2.6 µg/kg daily), in addition to metformin. After 12 weeks of treatment, mean HbA1c values dropped by 1.1% and 0.6% from baseline for high- and low-dose CJC-1131–treated subjects, respectively. Body weight declined in all 3 groups, but was greater in those who were treated with CJC-1131. Nausea primarily occurred during the first 4 weeks of treatment and, as in other members of this class, was the dominant side effect reported. No indications of local intolerance or immunogenicity were observed in this study.

Liraglutide

Liraglutide is a DPP-IV–resistant GLP-1 analog that is modified by the addition of a fatty acid group. This enables it to bind to serum albumin to slow the renal elimination of the drug. It appears to be suitable for once-daily administration. Early studies with liraglutide suggest that it had the capacity to regenerate pancreatic beta cells and reverse hyperglycemia in diabetic NOD mice and in vitro. These effects are potentiated when liraglutide is combined with gastrin. A recent industry-funded study randomized 210 subjects with type 2 diabetes to liraglutide once daily at various doses or metformin twice daily at 1000 mg for 12 weeks. Despite a mild decrease in weight, the mean HbA1c increased in those who were treated with liraglutide at all doses studied. The drug appeared to be safe in both younger and older populations, although nausea frequently was reported.

In general, the effects of these GLP-1 agonists on HbA1c are mild, and nausea is a limiting factor. However, the preponderance of clinical studies sug-
gests that they can reduce weight. More importantly, the studies indicate the potential to effectively harness the entero-pancreatic axis to improve physiologic insulin release, perhaps even to sustain or regenerate beta-cell mass. Although the agents studied thus far do not have the efficacy or tolerability to justify widespread use, this novel approach to diabetes therapeutics has great potential for the future.

**DPP-IV Inhibitors**

DPP-IV inhibitors are orally administered drugs that improve glycemic control by preventing the rapid degradation of the physiologically active incretin hormones GLP-1 and GIP. Sitagliptin and vildagliptin are 2 DPP-IV inhibitors that are being studied for the treatment of type 2 diabetes.

**Vildagliptin (LAF-237)**

Vildagliptin is a DPP-IV inhibitor that has demonstrated the intriguing ability to stabilize and augment beta-cell mass in animal studies. Although any theoretical beneficial effect on beta-cell function has yet to be examined in humans, vildagliptin has been studied in combination with metformin and pioglitazone in individuals with type 2 diabetes. In a study that randomized 107 subjects to metformin or metformin combined with vildagliptin, the addition of 50 mg daily of vildagliptin reduced HbA1c by an additional 1% and augmented postprandial insulin secretion. Subjects were followed for 1 year, in which the effect persisted. Combination therapy with pioglitazone appeared to be safe and effective over 4 weeks of study. Vildagliptin with pioglitazone reduced postprandial glucoses by 10% above the levels achieved by pioglitazone alone.

**Sitagliptin (MK-0431)**

Sitagliptin is a potent, orally active DPP-IV inhibitor. Preliminary human studies suggest that sitagliptin is safe and well tolerated at doses ranging from 10 to 600 mg per day. The drug appears to be effective in increasing postprandial GLP-1 levels by a factor of between 2 and 3, and in reducing postprandial glucose excursions. In a large dose-ranging study, 743 subjects were randomized to placebo, glipizide, or 1 of 4 doses of sitagliptin. Treatment with sitagliptin resulted in a mean improvement in HbA1c of between 0.4% and 0.8%, which was less than the 1% reduction achieved with glipizide. Treatment with glipizide resulted in an increase in weight of 1.1 kg, whereas all of the sitagliptin doses demonstrated weight neutrality. Hypoglycemia was less frequent in those who received sitagliptin. Furthermore, a 4-week trial of 50 mg of sitagliptin twice daily, in addition to metformin, demonstrated that the combination significantly improved fructosamine levels over metformin alone.

By enhancing the action of GLP-1, sitagliptin and vildagliptin appear to improve postprandial insulin release and to promote satiety that results in progressive weight loss. Both agents appear to have a low risk of hypoglycemia. Longer studies will illustrate their efficacy in reducing HbA1c alone and in combination with currently available oral hypoglycemics. A demonstration that DPP-IV inhibitors could enhance beta-cell mass by promoting proliferation, neogenesis, and survival in humans would likely catapult these oral agents into the mainstream and illustrate their potential use for diabetes prevention as well as treatment.

**Pramlintide**

Amylin is a 37-amino acid peptide that is produced by the pancreatic beta cell. Amylin is stored in beta-cell granules and cosecreted in a pulsatile manner with insulin in response to the same stimuli. Amylin levels are high in patients with insulin resistance and low or undetectable in patients with type 1 diabetes. Amylin inhibits glucagon secretion and induces satiety. A decrease in insulin- or glucose-induced glucose uptake in muscle has been noted with pramlintide. This indirect effect may contribute to insulin resistance and inhibition of glucose-stimulated insulin secretion. Amylin is unsuitable for pharmacologic use because of its tendency to form fibrils that can accumulate in the pancreas and accelerate beta-cell failure. Pramlintide is a stable analog of amylin that shares its actions and pharmacokinetic and pharmacodynamic properties. Pramlintide has been tested in several clinical studies, all of which were aimed at restoring amylin in absolute or relatively deficient patients with diabetes. The rationale for replacing amylin in patients with diabetes is to inhibit excessive postprandial glucagon secretion and delay gastric emptying. Pramlintide also may have a role in patients with type 2 diabetes as its use is associated with an improvement in satiety and weight loss.
Pramlintide has to be administered subcutaneously, typically before meals. Because it precipitates above pH 5.5, it is not licensed for combined use with insulin. Nevertheless, a recent study found that mixing insulin and pramlintide did not affect the pharmacodynamics of glucose or the pharmacokinetics of insulin or pramlintide in a clinically significant manner. This finding brings hope that multiple, extra injections may not be necessary for patients who could benefit from pramlintide.

Several clinical trials have demonstrated a small but consistent benefit of pramlintide on the HbA1c level in patients with either type 1 or type 2 diabetes without increasing the overall number of hypoglycemic events or inducing weight gain. For example, dosing pramlintide at 120 µg twice daily resulted in a reduction in mean HbA1c of 0.6% over placebo at 1 year in 656 subjects with type 2 diabetes, and was associated with a weight reduction from baseline of approximately 1.4 kg. The greatest weight loss occurred in patients with a body mass index of greater than 40 kg/m² and in patients taking metformin.

Despite these apparent benefits, the mean improvements in HbA1c were disappointing (mean reduction from baseline of 0.3%-0.6%), nausea was reported by approximately one third of subjects, there was an early risk of hypoglycemia in the weeks following initiation, and many subjects appeared to withdraw from these trials prematurely. Until well-tolerated insulin-amylin analog combinations are developed and demonstrated to have superior efficacy to insulin alone, there seems little justification for the widespread prescribing of this newly approved drug.

**NOVEL AGENTS TO COMBAT DIABETIC MICROVASCULAR COMPLICATIONS**

Protein kinase C (PKC) is a ubiquitous family of phospholipid-dependent serine/threonine kinases. Specific PKC isoforms are responsible for signal transduction for many physiological and pathological processes. Hyperglycemia appears to activate the PKC-beta isoform and, in doing so, may accelerate vascular damage in patients with diabetes through the increased synthesis of diacylglycerol. Vascular abnormalities associated with glucose-induced PKC activation include altered vascular blood flow, extracellular matrix deposition, basement membrane thickening, increased permeability, and neovascularization.

**RUBOXISTAURIN**

Ruboxistaurin is an orally effective PKC-beta-specific inhibitor. It has produced significant improvements in diabetic retinopathy, nephropathy, neuropathy, and cardiac dysfunction without toxicity in animal studies. It has reduced the development of diabetic vascular complications and has prevented hyperglycemia-induced impairment of endothelial-dependent vasodilation in healthy human subjects.

A recent placebo-controlled study examined the role of ruboxistaurin on visual loss in 252 patients with nonproliferative diabetic retinopathy. Over the 46 months of the study, 32 mg of ruboxistaurin significantly reduced the risk of visual loss, but had no effect on the rate of progression of diabetic retinopathy. Additionally, the role of ruboxistaurin in reducing the albumin excretion rate in patients with type 2 diabetes and nephropathy was studied in a phase 2 trial. The subjects who received 32 mg of ruboxistaurin demonstrated a 25% decline in the albumin excretion rate and preserved the glomerular filtration rate over 1 year. The study suggests that the addition of ruboxistaurin to therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or both had favorable effects on the albumin-creatinine ratio and glomerular filtration rate in persons with type 2 diabetes and nephropathy.

Other PKC inhibitors, such as pyridoxamine (an advanced glycation end-product [AGE] formation inhibitor) and alagebrium (an AGE cross-link breaker), are still under evaluation.

**SULODEXIDE**

Sulodexide is a heparinoid mixture of 3 glycosaminoglycans. It was shown to lower urinary albumin leakage and to diminish the thickening of glomerular capillary filtering membranes in animal models. Data of particular interest have demonstrated that sulodexide suppresses the hyperglycemia-induced overproduction of transforming growth factor-beta that is implicated in the induction of diabetic nephropathy.

When oral sulodexide was given to 223 patients with type 1 and type 2 diabetes with micro- or macroalbuminuria, the group that was treated with 200 mg daily was found to have albumin excretion rates reduced by 62%. As with ruboxistaurin, the effect was independent of coadministration of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors.
PPAR-ALPHA-DELTA AGONISTS

Although peroxisome-proliferator activated receptor (PPAR) alpha and gamma agonists are in widespread use for the treatment of hyperlipidemia and insulin resistance, respectively, the PPAR-delta agonists are still under study. PPAR-delta agonists, acting predominantly in skeletal muscle, have been shown to reduce triglyceride levels and small-dense low-density lipoproteins, as well as to increase high-density lipoprotein (HDL) levels. They may have an additional anti-inflammatory effect. Combined alpha-delta agonists may have a useful role in improving both glycemic and lipid control in patients with diabetes.

Muraglitazar is a combined PPAR-alpha-delta agonist that has entered clinical trials. A recent study randomized 1159 subjects with type 2 diabetes to receive either 5 mg of muraglitazar with metformin daily or 30 mg of pioglitazone with metformin daily.63 The results suggest a greater lowering of HbA1c with muraglitazar (–1.1%) as compared with the submaximal dose of pioglitazone (–0.9%). However, more patients treated with muraglitazar developed heart failure and hypoglycemia than those treated with pioglitazone. Improvements in HDL and reductions in triglycerides have been noteworthy with this drug.63,64

NOVEL INSULIN THERAPIES

EXUBERA

Pulmonary delivery of insulin offers a noninvasive alternative to injection as well as a rapid onset of action. In concert with the development of the inhalation technology, the actuator must be able to deliver flow-independent doses that are both uniform and reproducible. The device must be portable and accommodate a flexible dosing schedule. The drug must be stable at room temperature. It was necessary to create particles sized between 1 and 3 microns that could be delivered effectively to the deep lung for rapid drug absorption.65

Exubera, a rapid-acting insulin in powder form, is the most widely studied in patients with both type 1 and type 2 diabetes.66-68 The kinetics of inhaled insulin appear to have a more rapid onset than either subcutaneous insulin lispro or regular insulin, but time to maximal effect is intermediate between these two.69 The duration of action of Exubera was similar to regular insulin. Approximately 10 times the subcutaneously delivered dose needs to be inhaled for similar efficacy.69 When studied for over 6 months in 335 patients with type 1 diabetes, ultralente, in combination with inhaled insulin, had similar efficacy at reducing HbA1c as did a combination of neutral protamine hagedorn (NPH) and regular insulin. Similar results were noted in a study of 299 patients with type 2 diabetes.66

In both of these industry-supported studies, hypoglycemia was less common; however, cough was significantly more common in those who received the inhaled insulin. In patients with type 1 diabetes, the group who received inhaled insulin experienced a significant 4% reduction in the carbon monoxide diffusing capacity on pulmonary function testing without any clinical correlates.67 A similar decline was not noted in the study of patients with type 2 diabetes.66 Other pulmonary delivery technologies (including use of liquid insulin), such as those produced by AERx, ProMaxx, Spiros, and Technosphere, hold great promise for the future.66

INSULIN DETEMIR

Insulin glargine has been available since April 2000. As a basal insulin replacement, once-daily insulin glargine has a steady activity profile of over 24 hours without a pronounced peak. Insulin glargine appears to have clinical efficacy equal to NPH insulin, produces similar reductions in HbA1c and consistently reduces the incidence of nocturnal hypoglycemia in patients with type 1 and type 2 diabetes.71,72 Insulin detemir is an insulin analog created by acylation of the lysine-B29 amino acid residue that was recently approved by the FDA.71,72 It has been estimated that a dose of insulin detemir provides a 4.2-hour longer duration of action than does a similar dose of NPH (16.9 vs 12.7 hours).73 Two studies, each with 400 patients with type 1 diabetes, determined that when used in combination with insulin aspart, twice-daily insulin detemir had efficacy similar to twice-daily NPH in reducing HbA1c.74,75 Use of insulin detemir was not associated with any reduction in the overall rate of hypoglycemia, although the rate of minor hypoglycemia was reduced in 1 of the studies.74 The necessity for twice-daily dosing for insulin detemir may mitigate its widespread adoption for patients on basal-bolus insulin programs.

ISLET CELL TRANSPLANTATION

Islet cell transplantation has emerged as a viable, albeit short-term, treatment for patients with type 1
diabetes. In this procedure, islets are harvested from the donor’s pancreas and infused into the portal vein. Typically, infusions are needed from between 2 and 4 cadaveric donors to obtain insulin independence. The transplanted islets become lodged within the liver where they resume glucose-dependent insulin secretion. Lifelong immunosuppression is a necessary consequence of the procedure, and these medications frequently induce or exacerbate hypertension and hyperlipidemia. Currently, tacrolimus and sirolimus are coadministered and steroids are avoided. Although many patients with type 2 diabetes ultimately become insulin deficient, islet transplants have not been performed in this population. In Japan, where cultural considerations limit cadaveric donations, the feasibility of live-donor islet donation was recently demonstrated.

Despite these advancements, the long-term results have been disappointing. In March 2005, The Collaborative Islet Transplant Network reported on 86 recipients of islet infusions. At 6 and 12 months after the last infusion, 61% and 58% of the recipients were reported to be insulin independent. The median duration of insulin independence is approximately 15 months, and approximately 10% of patients remain insulin independent at 5 years. Although there were no deaths reported to the network, 45 serious adverse events were reported—a quarter of which were deemed to be life-threatening. The most frequent adverse events included intra-abdominal bleeding, portal vein thrombosis, liver function abnormalities, and complications related to immunosuppression.

**CONCLUSION**

The pipeline of novel therapeutics for diabetes care is robust. The incretin mimetics appear to be promising as they augment glucose-dependent insulin release, and may contribute to the preservation of pancreatic islets. However, the necessity for subcutaneous delivery and the frequency of nausea may mitigate broader utilization of GLP-1 agonists and drugs such as pramlintide. Inhibitors of DPP-IV have the advantage of being orally available, but have not been studied as widely.

Inhaled insulin has the potential to provide convenient mealtime insulin dosing. Exubera appears effective and safe with an attractive time-activity curve. Its utility may be determined by the effectiveness of the delivery device to consistently deliver doses independent of flow and to remain easily portable.

Although controlling glucose, blood pressure, and lipids as well as providing aspirin remains the mainstay of diabetes care when working to prevent both macro- and microvascular complications, a role for additional therapies, such as ruboxistaurin and sulodexide, may yet emerge after further studies clarify their role.

Currently, a cure for diabetes continues to elude us. These novel advances, as well as those that remain on the horizon, offer hope for a better life for the millions of people living with diabetes and for the hundreds of millions yet to be diagnosed.

**REFERENCES**


