Expanded Use of Exenatide in the Management of Type 2 Diabetes

Linda E. John, PharmD; Michael P. Kane, PharmD, FCCP, BCPS; Robert S. Busch, MD, FACE; and Robert A. Hamilton, PharmD

Exenatide is an incretin mimetic agent that possesses multiple mechanisms of glucose lowering. It enhances glucose-dependent insulin secretion by the pancreatic β-cell, leading to insulin release in the presence of elevated glucose concentrations. It also moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. Exenatide also slows gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation, thereby further decreasing postprandial blood glucose levels. Finally, administration of exenatide has been shown to reduce subsequent food intake by increasing satiety, often resulting in weight loss.[1]

Exenatide is indicated as an adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking metformin and/or a sulfonylurea but have not achieved adequate glycemic control.[1] To decrease gastrointestinal intolerance, exenatide is initiated at 5 μg subcutaneously twice daily and increased after 1 month to a target maintenance dose of 10 μg twice daily. Three 30-week studies as add-on therapy to sulfonylurea, metformin, and sufonylurea/metformin have demonstrated hemoglobin A_{1c} (A1C) reductions of ~ 1% with an average weight loss of 1.4–1.8 kg.[2–4] Therapy was generally well tolerated with the most frequent adverse events classified as mild or moderate and gastrointestinal in nature. Severe hypoglycemia was not observed during these studies.[2–4]

The concurrent use of exenatide with insulin, meglitinides, or α-glucosidase inhibitors has not been reported. Published information regarding the use of exenatide with thiazolidinediones (TZDs) is limited to two abstracts.[5,6] The objective of this study was to determine the effectiveness and safety of off-label exenatide use in patients with type 2 diabetes.

Methods

A retrospective review of the electronic medical records of one private-practice endocrinologist was conducted. The study was approved by the Albany College of Pharmacy investigational review board. The study population consisted of type 2 diabetic patients who were prescribed exenatide for off-label indications (i.e., exenatide was added to therapeutic regimens of patients receiving insulin, a TZD, a meglitinide, and/or an α-glucosidase inhibitor). Potential subjects were identified through a computerized text search of patient electronic medical records using the search terms "Byetta" and "exenatide." A data collection form was developed and used to collect the following information: baseline patient demographic information (sex, race, age, height, and weight), disease states, duration of diabetes, medications, laboratory information (A1C, cholesterol profile, and transaminase levels), blood pressure, duration of exenatide use, and adverse drug events.

Drug efficacy was evaluated by comparing each patient's baseline A1C, weight, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels), and blood pressure with data after a minimum of 100 days of exenatide use. Based on the American Diabetes Association (ADA) target A1C of < 7%, the percentage of patients achieving goal glycemic status before and after exenatide initiation was also compared. In addition, a comparison of diabetes medication use before and after exenatide initiation was performed. Drug effectiveness was evaluated in all patients with follow-up visits of a minimum of 100 days of therapy.

Drug safety was evaluated by review of transaminase levels and documented reports of side effects and/or drug discontinuation that occurred during therapy. Drug safety was evaluated in all patients in whom any follow-up data were available.

Statistical methods. Subjects served as their own controls; paired Student's *t* tests were used for statistical analysis. The binomial distribution was used to assess changes in the frequency of specific drug use between baseline and follow-up. *P* values < 0.05 were considered statistically significant.

Results

A total of 131 patients were prescribed off-label exenatide therapy. Follow-up data were available for 93 patients with a mean follow-up duration of 150 ± 32 days (range 100–231 days). Twenty-four patients did not have the necessary follow-up duration of 100 days though were presently receiving therapy with exenatide and reported no adverse effects; no follow-up information was available for five patients; and nine additional patients discontinued therapy because of adverse drug effects. Thirteen patients remained on the 5 μg twice daily dose because of gastrointestinal intolerance at the target 10 μg twice daily maintenance dose. Demographic information of the 93 patients is listed in Table 1. The

Table 1. Baseline Patient Characteristics

Characteristic	Value
n	93
Sex (M/F)	45/48
Race (white/African American/Asian)	80/12/1
Age (years)	61 ± 9.4
Duration of diabetes (years)	14 ± 8.5
Weight (kg)	111.3 ± 23.2
BMI (kg/m^2)	39.3 ± 7.6
A1C (%)	7.8 ± 1.4

Data are the means ± SD.

breakdown of off-label use, which illustrates a predominance of concomitant TZD (79.5%) and insulin (65.5%) therapies, is shown in Figure 1.

The effects of exenatide on A1C, weight, blood pressure, and cholesterol profiles are presented in Table 2. Use of exenatide was associated with significant reductions in A1C and weight and improvements in total cholesterol, triglycerides, and HDL cholesterol. There were no differences in mean blood pressure or LDL cholesterol at the end of the follow-up period compared with baseline. The percentage of patients achieving an A1C of < 7% did not significantly differ at follow-up (36.7%) compared with baseline (30.1%, $P > 0.05$). In addition, there were no differences in average A1C reduction or weight loss in the 13 patients who received 5 μg twice daily compared with those receiving 10 μg twice daily. Average weight loss was 4.9 kg (10.8 lb) with 86% of patients losing weight, 7.5% gaining weight, and 2.2% having no weight change. Follow-up weights were unavailable for 4 of the 93 (4.4%) patients.

Use of exenatide was associated with significant reductions of subsequent insulin, sulfonylurea, and meglitinide use. At baseline, 61 of 93 patients were insulin users compared with 57 of 93 at follow-up (including 3 patients not on insulin at baseline who started basal insulin therapy after the initiation of exenatide). The overall median number of daily insulin injections decreased from two (average 2.3 ± 1.4) to one (average 1.2 ± 1.0, $P < 0.001$). The average daily

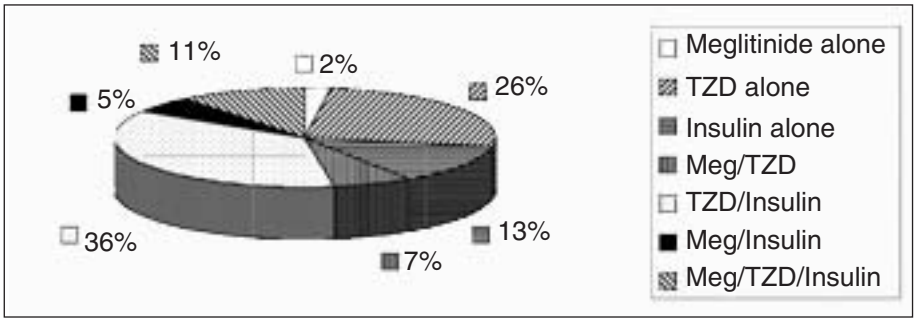

Figure 1. Off-Label Exenatide Use. Meg, meglitinide.

insulin dose decreased from 51 ± 46 to 42 ± 44 units ($P = 0.004$), and short-acting insulin doses decreased from 12 ± 16 to 4 ± 13 units ($P = 0.001$). There was no difference in average basal insulin dose (39 ± 37 compared with 38 ± 39 units. Of the 34 patients receiving bolus insulin at baseline, only 9 received bolus insulin therapy at follow-up ($P < 0.001$).

Compared to baseline, there was a significant decrease in the use of secretagogue therapy after exenatide initiation. Thirty-one patients received sulfonylurea therapy at baseline compared with 10 at follow-up ($P < 0.001$), and only 7 of the 23 patients receiving meglitinide at baseline continued therapy at follow-up ($P < 0.001$). In contrast, there was no significant difference in metformin or TZD use at follow-up compared with baseline.

Drug safety was evaluated by review of documented reports of side effects that occurred during exenatide therapy. Consistent with results of previous clinical studies, the most common side effects associated with exenatide in this study were nausea and vomiting. Nine patients (7.1%) discontinued therapy because of nausea or vomiting. In addition, nausea was reported by 8 patients who did not require exenatide discontinuation, and 13 patients could not tolerate a dosage increase to 10 μg twice daily because of gastrointestinal side effects. Hypoglycemia episodes (symptoms with or without documented glucose of < 60 mg/dl) were reported by three patients, but no cases of severe hypoglycemia (i.e., need for assistance of another person or hospitalization or emergency department visit) occurred. Hypoglycemia events occurred in patients receiving a meglitinide ($n = 1$) and insulin ($n = 2$). There were no increases in serum transaminase levels.

Discussion

Glucagon-like peptide-1 (GLP-1) is a naturally occurring 31–amino acid peptide secreted by L cells in the gas-

Table 2. Baseline and 1-Year Patient Characteristics

	Baseline	Follow-Up	*P* value*	*n*
A1C (%)	7.8 ± 1.4	7.4 ± 1.4	0.004	90
Weight (kg)	111.3 ± 23.2	106.4 ± 23.7	< 0.0001	89
Systolic blood pressure (mmHg)	116 ± 8.5	116 ± 9.2	0.9998	90
Diastolic blood pressure (mmHg)	71 ± 3.8	71 ± 5.2	0.9935	90
Total cholesterol (mg/dl)	50.8 ± 38.3	143 ± 35	0.0047	88
Triglycerides (mg/dl)	148 ± 78	135.2 ± 69.4	0.0276	87
LDL cholesterol (mg/dl)	69.7 ± 28.0	69.4 ± 28.5	0.9928	87
HDL cholesterol (mg/dl)	53.0 ± 13.5	46.6 ± 11.5	< 0.0001	87
Aspartate aminotransferase (units/l)	22.2 ± 11.9	21 ± 5.7	0.1406	
Alanine aminotransferase (units/l)	24.9 ± 13.2	23.9 ± 12.2	0.1892	88

Data are the means ± SD.
*Paired Student's *t* test.

trointestinal tract that stimulates insulin secretion in response to meals. Natural GLP-1 has a very short half-life because it is rapidly metabolized by dipeptidyl peptidase-IV (DPP-IV). Exenatide (exendin-4) is a synthetic 39–amino acid GLP-1 originally derived from the Gila monster lizard. It is structurally modified to resist breakdown by endogenous DPP-IV. Exenatide was approved by the U.S. Food and Drug Administration (FDA) in April 2005 as adjunctive therapy for the treatment of type 2 diabetic patients currently taking metformin and/or sulfonylurea and requiring additional glycemic control.[1] A request for an indication for use with a TZD (with or without metformin) is currently under review by the FDA. To date, there have been no published data regarding the use of exenatide in patients currently taking meglitinides, α-glucosidase inhibitors, or insulin. This retrospective study was completed to evaluate the off-label safety and efficacy of exenatide.

Three 30-week, placebo-controlled, double-blind, phase 3 studies of subjects with type 2 diabetes randomized to placebo, 5 μg of exenatide, or 10 μg of exenatide twice daily in patients already receiving metformin, a sulfonylurea, or a combination have been published.[2–4] In addition to differences in baseline antidiabetes medication use (in this study 80% of patients received a TZD and two-thirds received insulin at baseline), patients in this study were older (average 61 vs. 54 years of age), more obese (average BMI 39 vs. 34 kg/m^2), had a longer duration of diabetes (14 vs. 8 years), and had a lower baseline A1C (7.8 vs. 8.4%) compared with patients in the previously reported studies.

Our study found an average reduction in A1C of 0.4% compared with the 0.7 and 1% mean decreases in the 5 and 10 μg groups reported in the three prospective studies. In addition to the differences in patient populations mentioned above, other reasons for the apparent attenuated A1C effects found in this study could be related to the reduction in premeal insulin and secretagogue use that was empirically instituted at the start of exenatide therapy in our study population. In an abundance of caution to avoid hypoglycemia in patients who received exenatide in off-label indications, the secretagogue or bolus insulin was initially discontinued at the initiation of exenatide and then reinitiated only after the effect of exenatide was seen.

In our study, two-thirds of patients received insulin, one-third received sulfonylurea therapy, and 14% received a meglitinide at baseline. The exenatide package insert recommends a decrease in sulfonylurea dose at the initiation of exenatide therapy to reduce the risk of hypoglycemia; however, no recommendation exists regarding concurrent meglitinide or insulin therapy. The package insert of pramlintide, an amylin analog that has several pharmacological activities in common with exenatide, recommends a 50% decrease in premeal insulin doses when initiating therapy.[7] Because exenatide also possesses the additional mechanism of action of a glucose-dependent increase in insulin secretion, patients on premeal insulin or insulin secretagogues in this study were counseled to stop their premeal insulin or secreatagogue at the initiation of exenatide and titrate back if necessary. Indeed, sulfonylurea and meglitinide use decreased by 68 and 70%, respectively, and mean premeal insulin doses decreased by 67% from baseline to follow-up.

The combination of exenatide and TZD would seem to address the core defects of type 2 diabetes, i.e., β-cell dysfunction and insulin resistance. Two abstracts were recently published by Zinman et al.[5,6] evaluating the utility of exenatide in patients already receiving a TZD with or without metformin. On average, patients receiving exenatide decreased A1C 0.9% (from a baseline of 7.9%), reduced weight by 3 lb, and were almost four times as likely to reach an A1C of < 7% compared with placebo, with no significant difference in incidence of hypoglycemia.

Previous studies have demonstrated a significant A1C lowering of the 10-μg exenatide dose compared to the 5-μg dose,[2–4] although this was not observed in our study. The small number of patients (n = 13) maintained on the 5 μg dose and the potential of a type 2 error could explain this result.

The ADA recommends a target A1C of < 7%.[8] In this study, there was not a significant difference in the percentage of patients attaining this goal at follow-up (37%) compared with baseline (30%, P = 0.22). According to results of the National Health and Nutrition Examination Survey, target glycemic goal attainment in the United States decreased from 44% in 1994 to 37% in 2000.[9] A review of future A1C levels after the final manipulation of secretagogue and premeal insulin therapy will be of interest to assess the full utility of exenatide in these off-label combinations.

In addition to improved glycemic control, previous 30-week studies have demonstrated significant weight loss in exenatide-treated patients, including average weight reductions of 3.1 and 4.2 lb in the 5 and 10 μg exenatide groups, respectively, compared with an average loss of 1.4 lb in the placebo groups.[2–4] This study found an average 10.8-lb weight loss after an average of 150 days of exenatide use, with 86% of patients experiencing weight loss. That patient baseline weights were greater and baseline diabetes therapies used in this study (insulin and TZDs) are typically associated with greater weight gain compared to agents used in the previously published studies (sulfonylurea and metformin) may explain the greater weight loss identified in this study. Although prospective, open-label extension studies have demonstrated continued weight loss after 82 weeks of therapy with exenatide when used in combination with sulfonylurea or metformin (an average 8- to 10-lb weight loss was reported),[10] we plan to continue following this cohort of patients to evaluate the long-term effects of off-label exenatide use on weight.

Use of exenatide in this study was associated with an average 6.4 mg/dl decrease in HDL cholesterol, a 7 mg/dl decrease in total cholesterol, and a 13 mg/dl reduction in mean triglyceride levels. Although the reduction of HDL cholesterol is of some concern, especially in a disease considered to be a cardiovascular disease risk-equivalent,[11] HDL levels may transiently decrease early in weight loss and are reversible over time.[12] We will continue to monitor this study population to evaluate the long-term

effects of exenatide on HDL levels. Interestingly, HDL did not change in the prospective 30-week studies.[2–4] The changes in total cholesterol and triglycerides, though statistically significant, are probably not clinically significant.

The use of exenatide was not associated with blood pressure reduction in this study, despite the impressive average 10-lb weight loss associated with use of the drug. The fact that, on average, these patients' blood pressures were exquisitely controlled at baseline (116/71 mmHg) may explain this result.

Aggressive management of multiple cardiovascular risk factors in patients with type 2 diabetes has been associated with an impressive reduction of cardiovascular events.[13] Overall, the blood pressure and lipid control at baseline in this patient population were excellent, which required a mean of 2.3 antihypertensive and 1.5 anticholesterol medications per patient. Comparable to the results of the Steno 2 Study,[12] goal attainment of blood pressure and lipids in our patient population was more easily achieved than goal attainment of A1C. Exenatide represents an additional option to help achieve this elusive final goal, and we look forward to evaluating the long-term A1C effects of this drug in this population once patients are stabilized on a diabetes regimen.

Exenatide was reasonably well tolerated by patients in this study, with 26% of those with follow-up information reporting side effects, and only 9 of 126 patients (7.1%) discontinuing therapy. Previously reported studies were associated with a nausea prevalence of 36–51%, compared with a placebo rate of 7–23%, and a vomiting prevalence of 5–36% compared with a placebo rate of 3–13%.[2–4] Comparable to side effects reported in the prospective clinical trials, the most common side effects and reason for drug discontinuation in this study were gastrointestinal in nature.

Although dose titration of exenatide from 5 to 10 μg reduces the incidence of gastrointestinal side effects, it may also be advisable to have patients take the medication within 15 minutes before the start of a meal when initiating therapy (the package insert recommends taking exenatide 1–60 minutes before mealtime). Anecdotally, patients who take exenatide closer to meals reportedly have fewer incidences of gastrointestinal adverse effects. Once patients are tolerating the drug, moving the dose to 30–45 minutes before meals theoretically would be associated with greater drug efficacy. Clinical trials designed to determine optimal time of dosing before meals are reportedly ongoing.

Only three patients (2.4%) reported hypoglycemic reactions in this study. This compares to rates of 5–36% in the active treatment groups and 3–13% in the placebo groups of the randomized prospective studies.[2–4] Discontinuation of premeal insulin and insulin secretagogue at the initiation of exenatide presumably allowed this low frequency of adverse events. We would suggest this approach when considering exenatide in patients taking premeal insulin or insulin secretagogue therapy. The lack of other adverse effects or causes for drug discontinuation in this study attests to the overall tolerability and safety of this medication.

Type 2 diabetes is a progressive disease because of its characteristic insulin resistance, inappropriate hepatic glucose production, and decline in insulin secretion secondary to progressive pancreatic β-cell loss.[14] Any diabetes therapy that could change the natural progression of disease would be especially useful. TZDs are oral antidiabetes agents that act as peroxisome proliferator–activated receptor agonists. By activating these receptors, gene expression is induced, which leads to an improvement in insulin signaling, a decrease in peripheral insulin resistance, and an increase in glucose uptake by skeletal muscle, adipose tissue, and hepatic tissue. This distinct mechanism of action may help to preserve β-cell function and slow the progression to type 2 diabetes.[15–17] For these reasons, as well as because of their beneficial metabolic effects[18] and recent evidence pointing to cardioprotection,[19] there has been a call to consider TZD therapy as initial therapy in the management of type 2 diabetes.[20]

In vitro data have documented exenatide's ability to induce differentiation in pancreatic cell lines, causing a conversion of non–insulin-producing cell lines into cells that are capable of producing insulin and glucagon.[21] In addition, the administration of GLP-1 in animal studies resulted in pancreatic islet neogenesis, β-cell proliferation, and an increase in β-cell mass.[22] Although these findings have yet to be replicated in humans, the increase in β-cell mass combined with pancreatic cell differentiation highlight the potential of agents with GLP-1–like actions to target the progressive β-cell decline seen in those with type 2 diabetes, potentially leading to long-term improvements in patients treated with exenatide. Exenatide has been shown to augment phase 1 and phase 2 insulin release defects in patients with type 2 diabetes.[23]

Off-label combination of a TZD with exenatide is therefore particularly appealing. In addition to potentially halting the progression of diabetes, this combination would have a low risk of hypoglycemia, and exenatide would be expected to offset any TZD-associated weight gain. The off-label use of basal insulin with exenatide would offer another appealing diabetes treatment option, presumably offering a physiological basal-bolus approach to glycemic control (because these agents address fasting and postmeal glucose levels, respectively) with potentially less hypoglycemia and less weight gain than that occurring with traditional basal-bolus insulin regimens.

Conclusions

Off-label exenatide use was associated with significant A1C lowering and weight loss and was, overall, well tolerated. Randomized, prospective studies are needed to better evaluate the full utility of exenatide in patients receiving TZD and/or insulin therapy.

References

[1]Amylin Pharmceuticals: Byetta package insert. San Deigo, Calif., Amylin Pharmaceuticals, 2005

[2]Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, for the Exenatide-113 Clinical Study Group: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27:2628–2635, 2004

[3]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* 28:1092–1100, 2005

[4]Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: 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* 28:1083–1091, 2005

[5]Zinman B, Hoogwerf B, Garcia SD, Milton D, Giaconia J, Kim D, Brodows R: Safety and efficacy of exenatide in patients with type 2 diabetes mellitus (T2DM) using thiazolidinediones (TZDs) or TZDs and metformin (MET) [Abstract]. *Diabetes* 55 (Suppl. 1):A28, 2006

[6]Zinman B, Hoogwerf B, Garcia SD, Milton D, Giaconia J, Kim D, Trautmann M, Brodows R: Safety and efficacy of exenatide over 16 weeks in patients with type 2 diabetes mellitus using a thiazolidinedione with or without metformin [Abstract]. *Diabetologia* 49 (Suppl. 1):475–476, 2006

[7]Amylin Pharmaceuticals: Symlin package insert. San Diego, Calif., Amylin Pharmaceuticals, 2005

[8]American Diabetes Association. Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 28 (Suppl. 1):S4–S36, 2005

[9]Koro CE, Bowlin SJ, Bourgeois N, Fedder DO: Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care* 27:17–20, 2004

[10]Blonde L, Han J, Mac S, Poon T, Taylor K, Kim D: Exenatide reduced A1C and weight over 82 weeks in overweight patients with type 2 diabetes [Abstract]. *Diabetes* 54 (Suppl. 1): A118, 2005

[11]Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001

[12]Thompson PD, Jeffery RW, Wing RR, Wood PD: Unexpected decrease in plasma high density lipoprotein cholesterol with weight loss. *Am J Clin Nutr* 32:2016–2021, 1979

[13]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* 348:383–393, 2003

[14]Defronzo RA: Lilly Lecture 1987: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–687, 1988

[15]The Diabetes Prevention Program Research Group: Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program (DPP) [Abstract]. *Diabetes* 52 (Suppl.1):A58–A59, 2003

[16]Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002

[17]Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Kawakubo M, Buchanan TA: Effect of pioglitazone on pancreatic β-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* 55:517–522, 2006

[18]Parulkar AA, Pendergrass ML, Granda AR, Lee TR, Fonseca VA: Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 134:61–71, 2001

[19]Dormandy JA, Charbonnel B, Eckland DA, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, MokáÀ M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, TatoÀ J, on behalf of the PROactive Investigators: Secondary prevention of secondary events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised, controlled trial. *Lancet* 366:1279–1289, 2005

[20]Kendall KM: Thiazolidinediones: the case for early use. *Diabetes Care* 29:154–157, 2006

[21]Zhou J, Wang X, Pineyro MA, Egan JM: Gucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon- and insulin-producing cells. *Diabetes* 48:2358–2366, 1999

[22]Zhou J, Pineyro MA , Wang W, Doyle ME, Egan JM: Exendin-4 differentiation of a human pancreatic duct cellline into endocrine cells: involvement of PDX-1 and HNF3β transcription factors. *J Cell Physiol* 192:304–314, 2002

[23]Fehse F, Trautmann M, Holst JJ, Halseth AE, Nanayakkara N, Nielsen LL, Fineman MS, Kim DD, Nauck MA: Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 90:5991–5997, 2005

At the time of this writing, Linda E. John, PharmD, was a pharmacy resident at Albany College of Pharmacy and The Endocrine Group in Albany, N.Y. She is currently a clinical pharmacist at United Memorial Hospital in Batavia, N.Y. Michael P. Kane, PharmD, FCCP, BCPS, is an associate professor in the Department of Pharmacy Practice of Albany College of Pharmacy and a clinical pharmacy specialist at The Endocrine Group. Robert S. Busch, MD, FACE, is an attending physician at The Endocrine Group. Robert A. Hamilton, PharmD, is a professor at the Albany College of Pharmacy.

Note of disclosure: *Dr. Busch is a stock shareholder in Amylin Pharmaceuticals and has received honoraria for speaking engagements from Eli Lilly & Company. These two companies market exenatide for the treatment of diabetes. Dr. Busch and Dr. Kane serve on a speaker's bureau for Takeda, which manufactures a TZD for the treatment of diabetes.*