Treating Diabetes by Modifying GLP-1 Activity: Current Options and New Developments

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STATEMENT OF NEED

In 2005, the first drug in the class of glucagon-like peptide 1 (GLP-1) analogues was approved by the US Food and Drug Administration (FDA): Exenatide (Byetta, Eli Lilly). There is a substantial body of recently published studies describing the results, side effects and effective clinical use of the drug. Other GLP-1 analogues, as well as drugs that act by inhibiting dipeptidyl peptidase-IV (DPP-IV, which degrades GLP-1), are now in later-phase clinical development and expected to enter the market over the next few years. Clinicians should familiarize themselves with the data showing how these new medications may benefit their patients.

TARGET AUDIENCE

This activity is designed for primary care physicians, podiatrists, neurologists and other practitioners treating patients with diabetes and diabetic complications.

LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- Describe the mechanism of action, indications, adverse effects and clinical results of exenatide;
- Describe the most recent clinical study data on the safety and efficacy of other GLP-1 analogues; and
- Describe the mechanisms of action and most recent clinical study data on the safety and efficacy of DPP-IV inhibitors.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Participants have a choice of completing this activity online by visiting www.DiabeticMCToday.com; getting real-time results at www.CMEToday.net; or by using the print forms following this activity.

Upon completing the activity and achieving a passing score of ≥70% on the self-assessment test, participants will receive a CME credit letter awarding *AMA/PRA Category 1 Credit™* 4 weeks after the registration and evaluation materials are received. The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and Diabetic Microvascular Complications Today.

The Dulaney Foundation designates this educational activity for a maximum of *1 AMA/PRA Category 1 Credit.™* Physicians should only claim credit commensurate with the extent of their participation in the activity.

TABLE 1. RESULTS OF CLINICAL STUDIES OF EXENATIDE 10 µg OR 5 µg T.I.D. IN PATIENTS TAKING SULFONYLUREA, METFORMIN OR BOTH

Study	Sulfonylurea[13]			Metformin[12]			Sulfonylurea + metformin[14]		
Subgroup	10 µg	5 µg	Placebo	10 µg	5 µg	Placebo	10 µg	5 µg	Placebo
HbA1c (mean ±SE)	-0.86 ±0.11%	-0.46 ±0.12%	+0.12 ±0.09%	-0.78 ±0.10%	-0.40 ±0.11%	+0.08 ±0.10%	-0.80 ±0.10%	-0.60 ±0.10%	+0.20 ±0.10%
Patients achieving final HbA1c ≤7% (baseline >7%)	41%	33%	9%	46%	32%	13%	34%	27%	9%
Weight (mean ± SE)	-1.6 ± 0.30 kg	-0.90 ±0.27 kg	-0.60 ±0.30 kg	-2.8 ± 0.50 kg	-1.60 ± 0.40 kg	-0.30 ±0.30 kg	-1.60 ±0.20 kg	-1.60 ±0.20 kg	-0.90 ±0.20 kg

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services that relate to the content of their presentation/material or the commercial contributors of this activity; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

None.

FACULTY CREDENTIALS

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INTRODUCTION

One of the more recent avenues for the development of medical therapies for diabetes has focused on the activity of glucagon-like peptide 1 (GLP-1), an incretin that stimulates glucose-dependent insulin secretion from pancreatic islet cells.[1] GLP-1 is produced by the proglucagon gene in L-cells of the small intestine upon stimulation by nutrient ingestion.[2] Because GLP-1 production decreases with the onset of type 2 diabetes, it has been investigated as a possible target for new diabetes therapies.[3]

One advantage of targeting GLP-1 is that its activity has been found to be independent of the severity or duration of diabetes.[4] Direct administration of GLP-1 is problematic, however, because it is quickly degraded (plasma half-life is approximately 90 seconds) by dipeptidyl peptidase IV (DPP-IV) and cleared by the kidneys.[5,6] As a result, new drug research has focused on developing analogues of GLP-1 that are longer-lasting and also on finding agents that inhibit the activity of DPP-IV.

EXENATIDE

The first GLP-1 analogue to be approved by the FDA is exenatide (Byetta, Amylin/Eli Lilly, San Diego and Indianapolis, Ind).[7] Exenatide injection is approved as adjunctive therapy for patients with type 2 diabetes with inadequate glycemic control on metformin, a sulfonylurea, or both. Exenatide has not yet been approved for use with insulin. The recommended initial dosage of exenatide is 5 µg b.i.d. (within 1 hour before morning and evening meals), increasing to 10 µg b.i.d. if glycemic control is not achieved.

Exenatide is a synthetic version of exendin-4, a naturally occurring component of Gila monster saliva that shares a 53% sequence identity with GLP-1.[8] An amino acid substitution makes exenatide relatively resistant to DPP-IV, thus prolonging its plasma half-life,[9] however, exenatide still exhibits the same type of dose-dependent and glucose-dependent activity as GLP-1 in increasing insulin secretion.[10] Like GLP-1, exenatide also slows gastric emptying, inhibits inappropriate glucagon release in the fasting state (making it the only available diabetes therapy that targets glucagon), and can produce weight loss in patients with diabetes.[11,12] In animal models, it has been shown to slow or reverse the progression of diabetes.

Three 30-week, randomized, placebo-controlled, clinical trials examined the results of adding a 5- or 10-µg b.i.d. dose of exenatide to a sulfonylurea, metformin, or both in patients with type 2 diabetes.[12-14] Key results of these studies are summarized in Table 1.

The placebo-adjusted change in HbA1c with the 10-µg exenatide dosage was -0.98% when added to sulfony-

lurea alone, -0.86% when added to metformin alone, and -1.0% when added to a combination of sulfonylurea and metformin. The effect was not as great in the subgroups receiving the lower dose, but all differences between treatment and placebo groups were statistically significant at a minimum level of $P<.002$.

In patients whose baseline HbA1c level was >7%, a final HbA1c of <7% was achieved by approximately 2.5 to 4.5 times as many patients in the treatment groups versus the control groups, with the results again being dose-dependent.

Weight loss was also significantly greater in the treatment groups. Although nausea was the most frequent adverse event resulting in withdrawal from the study, weight loss was not found to be correlated with the occurrence of nausea. Nausea was generally reported as mild to moderate, and tended to diminish with ongoing treatment. In another study, dose titration was found useful in reducing nausea.[15]

The occurrence of mild to moderate hypoglycemic events was greater in treatment groups receiving sulfonylureas, but not in those on metformin alone. Hypoglycemia was more frequent in patients with HbA1c close to 7% and less frequent in patients on minimum doses of sulfonylureas. Reducing the dose of sulfonylureas may thus help to prevent hypoglycemia.

Longer-term data from open-label extension trials were recently published.[16] The study population included patients enrolled in the phase 3 sulfonylurea and sulfonylurea-plus-metformin groups. The initial 30-week trials were extended with 52-week open-label, uncontrolled studies in which all patients received the 10-µg b.i.d. dosage of exenatide along with previous oral medication(s). Data at the 82-week follow-up point were available for 222 patients.

The reduction in HbA1c level seen at the end of the initial 30-week study was sustained through the 52-week extension study (-1.0 ±0.10%). Of 207 patients with baseline HbA1c >7%, 36% had reached <7% at 30 weeks, a proportion that increased to 44% by the end of the extension study. Even larger reductions were seen in patients with baseline HbA1c >9%, who had a change of -1.9 ±0.2%.

Reduction in body weight continued throughout the extension study, reaching a mean 4.1% reduction from baseline at the 82-week point. Patients with higher body mass index at baseline tended to show greater weight reduction by the end of the study period.

Results from a similar open-label extension of the phase 3 metformin-only group have not yet reached publication.

LIRAGLUTIDE

Another GLP-1 analogue that is still in clinical trials is liraglutide (NN2211; Novo Nordisk, Bagsvaerd, Denmark). Liraglutide is an acylated GLP-1 derivative that binds to albumin, which inhibits its degradation. A safety and tolerability study reported an elimination half-life of 11 to 15 hours after subcutaneous administration, suggesting the potential for once-daily dosing.[17] Another study found that a single bedtime dose of 10 µg/kg liraglutide reduced fasting and postprandial glucose levels, increased insulin secretion, and delayed gastric emptying throughout the following day.[18] No cases of hypoglycemia were reported, although two of the 11 patients experienced nausea.

Another study randomized 190 patients with type 2 diabetes to receive one of five doses of liraglutide (0.045, 0.225, 0.45, 0.60 or 0.75 mg once a day before breakfast), placebo, or glimepiride for 12 weeks.[19] At 12 weeks, HbA1c was decreased from baseline in all groups except patients receiving the lowest dosage of liraglutide. The two groups receiving the highest dosage of liraglutide had HbA1c reductions similar to those seen in the group receiving the maximally tolerated glimepiride dose; those patients receiving liraglutide at 0.60 mg or 0.75 mg or glimeperide had significantly greater reductions in HbA1c than the placebo group.

Body weight decreased in patients receiving liraglutide, with higher dosages tending to produce greater weight loss. Patients on placebo had little change in weight, and those on glimepiride tended to gain weight.

Of the 135 patients in all liraglutide groups, one experienced mild hypoglycemia (defined as blood glucose <2.8 mmol/L) and seven reported hypoglycemic symptoms but did not meet the study protocol's definition of hypoglycemia. The most frequently reported adverse events were headache and nausea, which were described as mild to moderate in all cases. Nausea occurred more often in patients receiving higher doses of liraglutide. No patients discontinued the study due to these events.

Another double-blind study randomized 210 patients who were receiving 1,000-mg b.i.d. of metformin to either continue metformin or change to one of five doses (again between 0.045 mg and 0.75 mg daily) of liraglutide for 12 weeks.[20] The two lowest-dose groups failed to achieve the same level of glycemic control or HbA1c reduction as the metformin group, however, fasting plasma glucose and HbA1c levels in the three highest-dose groups were equivalent to the metformin group. No major hypoglycemic events were reported in any group, and the most common adverse event was nausea.

There are other GLP-1 analogues in early clinical trials, but very little data has been published in peer-reviewed literature.

DPP-IV INHIBITORS

Another means of increasing GLP-1 may be to inhibit the activity of the enzyme DPP-IV, a ubiquitous enzyme that serves as the major means of GLP-1 degradation.[21] DPP-IV also deactivates glucose-dependent insulinotropic peptide (GIP), another insulinotropic incretin hormone. DPP-IV inhibitors may therefore address the growing understanding of diabetes as a multihormonal disease.[22] The ability of metformin to produce a modest increase in GLP-1 secretion suggests that it might work synergistically with a DPP-IV inhibitor.[23]

DPP-IV inhibitors can be formulated for oral administration, and several are currently in clinical trials or awaiting FDA approval.

The new drug application for sitagliptin (Januvia; Merck, Whitehouse Station, NJ) was submitted for FDA review in early 2006. Sitagliptin is specific to both GLP-1 and GIP. A randomized, double-blind, placebo-controlled trial of 743 patients showed a 0.77% drop in HbA1c during 12 weeks and no significant weight gain or loss in patients receiving sitagliptin compared with placebo.[24] Patients receiving maximal-dose glipizide had a 1.0% drop in HbA1c and a 1.1 kg weight gain. Gastrointestinal side effects were similar in both groups.

Vildagliptin (LAF237; Novartis, Basel, Switzerland) is currently in phase 3 clinical trials. In a double-blind study, 107 patients previously receiving metformin monotherapy were randomized to metformin plus either placebo or once-daily vildagliptin 50 mg.[25] After 12 weeks, there was a -0.6 ±0.1% change in HbA1c in the treatment group and no change in the placebo group. A 40-week open-label extension of the study found a difference between the two groups of -1.1 ±0.2% in HbA1c. This was the result of an increase in the placebo group, while the treatment group remained stable. There was no difference in body weight between the two groups.

Saxagliptin (BMS-477118; Bristol-Myers Squibb, Princeton, NJ) is a DPP-IV inhibitor that was found to be highly efficacious, stable, and long-acting in preclinical studies.[26] It is currently in phase 3 trials, but no data from clinical studies have yet been published in the peer-reviewed literature.

Overall, the DPP-IV inhibitors that have undergone clinical trials are well tolerated Unfortunately, they do not seem to achieve the same degree of efficacy as GLP-1 analogues, nor do they produce weight loss. Oral administration, however, may render them future agents of choice.

Diabetes is increasingly recognized as a multihormonal disease. As a result of multiple novel mechanisms of action, GLP-1 based therapies bridge the gaps in diabetes therapy. ■

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CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. Which of the following statements about GLP-1 is NOT accurate:
a. GLP-1 stimulates pancreatic insulin secretion.
b. GLP-1 production is stimulated by the ingestion of nutrients.
c. In type 2 diabetes, GLP-1 production decreases.
d. In longstanding or severe diabetes, the effect of GLP-1 decreases.

2. The FDA-approved indications for exenatide include which one of the following:
a. Primary therapy for type 2 diabetes.
b. Adjunctive use with insulin.
c. Adjunctive use with metformin, a sulfonylurea, or both.
d. Adjunctive use with any other diabetes medications when glycemic control is inadequate.

3. In the 30-week phase 3 clinical studies, adding exenatide 10 µg b.i.d. to sulfonylureas, metformin, or both provides an additional lowering effect of HbA1c levels by approximately:
a. 0.5%
b. 1.0%
c. 1.5%
d. 2.0%

4. In those studies, the weight loss seen with exenatide versus placebo was found to be:
a. Statistically significant in all treatment groups.
b. Statistically significant only when used with both sulfonylureas and metformin.
c. Limited to the initial treatment period.
d. Associated with nausea.

5. In the 52-week extension study of exenatide plus sulfonylureas or sulfonylureas plus metformin, patients with baseline HbA1c >9% had:
a. Smaller reductions than patients with baseline >7%.
b. Approximately the same reduction as patients with baseline >7%.
c. Approximately twice as great a reduction as patients with baseline >7%.
d. Approximately three times are great a reduction as patients with baseline >7%.

6. Which of the following statements about liraglutide is NOT accurate:
a. It is an albumin-binding GLP-1 analogue.
b. Once-a-day dosing is possible.
c. At sufficient dosages, it can produce weight loss.
d. Nausea has not been noted as an adverse event.

7. DPP-IV:
a. Is the major agent responsible for degrading GLP-1.
b. Deactivates GIP.
c. Is present in many tissues.
d. All of the above.

8. As compared with GLP-1 analogues, DPP-IV inhibitors:
a. Produce a smaller reduction in HbA1c levels.
b. Achieve similar weight loss.
c. Have a much greater percentage of patients with nausea.
d. All of the above.

REGISTRATION/EVALUATION FORM: TREATING DIABETES BY MODIFYING GLP-1 ACTIVITY

To obtain AMA/PRA category 1 credit, you must:

- Read the learning objectives and the CME article and complete the self-assessment test.
- Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
- Send the Registration/Evaluation form to **The Dulaney Foundation, PO Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.**
- Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 47.

1. A B C D	2. A B C D	3. A B C D	4. A B C D	5. A B C D
6. A B C D	7. A B C D	8. A B C D		

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an educational grant from Eli Lilly and Company.

I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ **Date** _____

Credit for this activity is available until June 31, 2007.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES

After successful completion of this program, you should be able to:

• Describe the mechanism of action, indications, adverse effects and clinical results of exenatide.	5	4	3	2	1
• Describe the most recent clinical study data on the safety and efficacy of other GLP-1 analogues.	5	4	3	2	1
• Describe the mechanism of action and most recent clinical trial data on the safety and efficacy of DPP-IV inhibitors.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

• The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
• The information presented will influence how I practice.	5	4	3	2	1
• The information presented will help me improve patient care.	5	4	3	2	1
• The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
• The program was educationally sound and scientifically balanced.	5	4	3	2	1
• The program avoided commercial bias or influence.	5	4	3	2	1
• Overall, the program met my expectations.	5	4	3	2	1
• I would recommend this program to my colleagues.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

- If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____
- Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____

_____