

# CE IN THE MORNINGS

A Tradition of Outstanding Pharmacy Education

## New and Emerging Incretin-based Therapies as Part of Rational Combination Therapy for Type 2 Diabetes

The selection of glycemic goals and appropriate combination drug therapy for type 2 diabetes, including new and emerging diabetes agents, based on patient characteristics were the subject of one of four CE in the Mornings topics at the 46th ASHP Midyear Clinical Meeting and Exhibition in New Orleans, Louisiana, in December 2011. The program was presented by Susan Cornell, Pharm.D., CDE, FAPhA, FADE. In a live webinar conducted on March 8, 2012, Dr. Cornell illustrated the principles used to select therapeutic goals and devise a pharmacotherapy plan in several patient cases. Some of the highlights of the webinar pertaining to factors to consider when establishing glycemic goals and selecting appropriate drug therapy for type 2 diabetes based on patient characteristics were described in an [earlier e-Newsletter](#) (PDF). Rational combination therapy and new and emerging incretin-based therapies for type 2 diabetes are described in this e-Newsletter.

### Initiative Faculty

**Susan Cornell, Pharm.D., CDE, FAPhA, FADE**

Assistant Director of Experiential Education

Associate Professor of Pharmacy Practice

Midwestern University Chicago College of Pharmacy

Downers Grove, Illinois

## Expand Your Knowledge



### On-demand CPE Activities

If you were unable to attend the live symposium, *Diabetes: Exploring the Risks and Benefits of Emerging Type 2 Therapies*, conducted at the 2011 ASHP Midyear Clinical Meeting, a **1-hour CPE activity is available on demand**.



### Faculty Podcast Interviews

Visit the CE in the Mornings [web portal](#) to listen to podcast interviews with the faculty. Four interviews, each lasting approximately 5 to 14 minutes, are available.

Monotherapy with oral agents rarely is effective for achieving glycemic control over the long term in patients with type 2 diabetes. Most patients with an A1c greater than 7.5% require combination therapy using agents with complementary mechanisms of action.<sup>1</sup> Rational combination therapy entails the use of drugs that improve control of both fasting and postprandial plasma glucose (Table 1). Type 2 diabetes is a chronic disease associated with defects in multiple organs, including the pancreas, liver, peripheral tissues, gastrointestinal (GI) tract, adipose tissues, brain, and possibly the kidneys.<sup>2</sup> Agents that target different organ defects should be selected to optimize therapeutic outcomes.

Table 2 lists combination therapy options based the magnitude of A1c reduction needed to achieve therapeutic goals and an algorithm for glycemic control from the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology.<sup>3</sup> The American Diabetes Association recommends a target A1c less than 7.0%, and AACE recommends a target A1c less than 6.5%.<sup>1,4</sup> Insulin usually is needed for patients who need a reduction in A1c of more than 2% because the A1c reduction provided by other

therapies is insufficient even when non-insulin agents are used in combination. Fasting plasma glucose should be addressed before postprandial plasma glucose in these patients because the latter will decrease when the former decreases.

## Question: What is the role of incretin-based therapy in treating type 2 diabetes?

Incretins are GI hormones that enhance the secretion of insulin after the ingestion of food, thereby minimizing postprandial hyperglycemia. The incretin effect in response to meals is diminished in patients with type 2 diabetes, possibly because of reduced incretin secretion or decreased responsiveness of pancreatic  $\beta$  cells to incretins. Glucagon-like peptide (GLP)-1 agonists and inhibitors of the enzyme dipeptidyl peptidase (DPP)-4, which inactivates GLP-1, have been developed to treat type 2 diabetes.

**Table 1.**  
Differences Among Diabetes Drugs and Drug Classes in Effects on Plasma Glucose

Fasting	<ul style="list-style-type: none"> <li>• Insulin (intermediate- and long-acting)</li> <li>• Metformin (a biguanide)</li> <li>• Sulfonylureas</li> <li>• Thiazolidinediones (i.e., pioglitazone)</li> <li>• Colesevelam (a bile acid sequestrant)</li> <li>• Long-acting GLP-1 agonists (e.g., once-weekly exenatide, once-daily liraglutide)</li> </ul>
Postprandial	<ul style="list-style-type: none"> <li>• Insulin (regular, rapid-acting)</li> <li>• Pramlintide (an amylinomimetic)</li> <li>• <math>\alpha</math>-glucosidase inhibitors (e.g., acarbose, miglitol)</li> <li>• Meglitinides (e.g., nateglinide, repaglinide)</li> <li>• DPP-4 inhibitors (e.g., linagliptin, saxagliptin, sitagliptin)</li> <li>• Short- and long-acting GLP-1 agonists (e.g., twice-daily and once-weekly exenatide, once-daily liraglutide)</li> <li>• Bromocriptine (a dopamine agonist)</li> <li>• Sulfonylureas</li> <li>• Thiazolidinediones (i.e., pioglitazone)</li> </ul>

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide

**Table 2.**  
Combination Therapy Options Based on Magnitude of A1c Reduction Needed<sup>3</sup>

Magnitude of A1c Reduction Needed (%)	Combination Therapy Options
<1 <sup>a</sup>	Biguanide + TZD Biguanide + DPP-4 inhibitor Biguanide + GLP-1 agonist (short-acting <sup>b</sup> )
1-2 <sup>a</sup>	Biguanide + TZD Biguanide + GLP-1 agonist (short- or long-acting <sup>b</sup> ) Biguanide + TZD + GLP-1 agonist (short- or long-acting <sup>b</sup> ) Biguanide + TZD + DPP-4 inhibitor
>2 <sup>c</sup>	Biguanide + DPP-4 inhibitor + basal insulin Biguanide + GLP-1 agonist (short- or long-acting <sup>b</sup> ) + basal insulin Biguanide + TZD + basal insulin Basal insulin + bolus insulin Biguanide + basal insulin + bolus insulin

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; TZD = thiazolidinedione

<sup>a</sup> Postprandial glucose should be addressed as well as fasting glucose. Basal insulin can be added to any of the combinations if needed.

<sup>b</sup> Conventional twice-daily exenatide is a short-acting GLP-1 agonist. Long-acting GLP-1 agonists include once-daily liraglutide and a once-weekly form of exenatide approved by the Food and Drug Administration in January 2012.

<sup>c</sup> Fasting plasma glucose should be addressed before postprandial plasma glucose.

## Question: How are GLP-1 agonists and DPP-4 inhibitors similar, and how do these classes of drugs differ?

Similarities among GLP-1 agonists (e.g., exenatide, liraglutide) and DPP-4 inhibitors (e.g., sitagliptin, saxagliptin, linagliptin) include their pharmacologic effects to improve  $\beta$ -cell function and promote glucose-dependent insulin secretion, resulting in substantial improvements in A1c and postprandial and fasting glucose concentrations.<sup>5-10</sup> The reduction in A1c observed during separate clinical studies was greater from GLP-1 agonists (0.8% to 1.8%) than from DPP-4 inhibitors (0.5% to 1.1%).<sup>5</sup> Hypoglycemia is not typically associated with GLP-1 agonists or DPP-4 inhibitors when the drugs are used alone (hypoglycemia can occur when the drugs are used in combination with other diabetes agents that cause hypoglycemia).

The route of administration is an important difference between GLP-1 agonists, which are given by subcutaneous injection, and DPP-4 inhibitors, which are taken orally. The DPP-4 inhibitors are not merely oral forms of GLP-1 agonists. Treatment with GLP-1 agonists produces pharmacologic concentrations of GLP-1 in patients with diabetes that are 6- to 10-fold higher than the physiologic concentrations observed in

the postprandial state in healthy people, which contributes to the reduction in A1c and adverse effects during GLP-1 agonist therapy.<sup>5</sup> By contrast, DPP-4 inhibitor therapy produces physiologic concentrations in patients with diabetes that are 2- to 3-fold higher than the concentrations observed in the postprandial state in health individuals, which may result in a smaller reduction in A1c and minimal risk of adverse effects compared with GLP-1 agonists.

The GLP-1 agonists slow gastric emptying, which can lead to early satiety, reduced appetite, nausea, and weight loss.<sup>5</sup> Eating small, frequent meals instead of fewer meals with larger portions during GLP-1 agonist therapy can minimize the nausea. The DPP-4 inhibitors have minimal effects on gastric emptying and are weight neutral.

## Question: How do the new and emerging GLP-1 agonists differ?

The new and emerging GLP-1 agonists differ in their pharmacokinetics and frequency of administration (Table 3). The twice daily form of exenatide has a short half-life and primarily affects postprandial plasma glucose. The long-

**Table 3.**  
**Pharmacokinetics of New and Emerging GLP-1 Agonists<sup>11-17,a</sup>**

Agent (Frequency of Administration)	Description	T <sub>max</sub>	t <sub>1/2</sub>	Active Metabolites/Major Drug Interactions	Elimination
<i>FDA-Approved Agents</i>					
Exenatide (conventional twice daily)	Synthetic analog of exendin-4 protein found in saliva of <i>Heloderma suspectum</i> (lizard); 53% homology to native GLP-1	2.1 hr	2.4 hr	None	Mainly renal; not recommended for patients with ESRD or severe renal impairment
Exenatide QW (once weekly)	Exenatide suspended in PLG microspheres	2-5 weeks	NR	None	Renal
Liraglutide (once daily)	Acylated analog of human GLP-1; 97% homology to native GLP-1	8-12 hr	13 hr	None	Mainly metabolized by proteolytic degradation; use caution in patients with renal impairment
<i>Agents Pending FDA Approval</i>					
Albiglutide (once weekly)	GLP-1 dimer genetically fused to human albumin	3-5 days	6-7 days	NR	NR
Dulaglutide (once weekly)	GLP-1 IgG4-Fc fusion protein	~70 hr	~4 days	NR	NR
Lixisenatide (once daily)	Exendin-4-like GLP-1 agonist modified C-terminally	~2 hr	~3 hr	NR	Renal

ESRD = end-stage renal disease; FDA = Food and Drug Administration; GLP = glucagon-like peptide; PLG = poly-(D,L-lactide-co-glycolide); NR = not reported

<sup>a</sup>All agents are given by subcutaneous injection.

acting GLP-1 agonist liraglutide is given once daily. A once-weekly form of exenatide was approved by the Food and Drug Administration (FDA) in late January 2012.<sup>18</sup> Additional long-acting, injectable GLP-1 agonists are in development, including lixisenatide, which is used once daily despite its short half-life, and albiglutide and dulaglutide, which are used once weekly.<sup>19,20</sup> Long-acting GLP-1 agonists affect both fasting and postprandial plasma glucose.

### Question: How do the new and emerging DPP-4 inhibitors differ?

Three DPP-4 inhibitors (linagliptin, saxagliptin, and sitagliptin) currently are available in the United States. The investigational DPP-4 inhibitor alogliptin was reviewed by FDA in April 2012, but it was not approved at that time. FDA has requested more information from the manufacturer.

The pharmacodynamics and pharmacokinetics of the new and emerging DPP-4 inhibitors are fairly similar (Table 4). They are administered orally once daily and have similar efficacy in improving glycemic control without causing weight gain.<sup>21</sup> Interactions with drugs that induce or inhibit cytochrome P-450 3A4 enzymes are a potential concern for patients receiving linagliptin or saxagliptin, respectively.<sup>22,23</sup> Reduction in the dosage of saxagliptin and sitagliptin is recommended for patients with renal impairment.<sup>23-25</sup>

### Practice Changes Related to Treating Type 2 Diabetes

In a survey conducted approximately 8 weeks after the December 2011 CE in the Mornings program on type 2 diabetes, program attendees were asked what practices they had implemented or improved based on the knowledge acquired by participating in the program. Many attendees had already made improvements or implemented practices to improve drug therapy in this patient population. These practices include:

- Considering evidence-based guidelines when determining glycemic goals (e.g., A1c, fasting and postprandial blood glucose) for patients with type 2 diabetes,
- Recommending pharmacotherapy based on patient-specific factors (e.g., duration of diabetes, presence of other medical conditions),
- Recommending individualized clinical goals (e.g., A1c, blood pressure) based on patient-specific factors (e.g., duration of diabetes, quality of past glycemic control, patient tolerability, quality of life),
- Evaluating the benefits of appropriate combination drug therapy (targeting different dysfunctional organs) in patients with type 2 diabetes, and
- Considering  $\beta$ -cell preservation, risk of hypoglycemia, and risk of weight gain when initiating drug therapy in patients with type 2 diabetes.

Barriers to implementation of or improvement in practices reported by survey respondents included a lack of time, personnel, administrative support, experience, and financial resources. Information on type 2 diabetes provided in the CE in the Mornings educational initiative should help overcome some of these barriers and improve patient care and outcomes.

**Table 4.**  
**Pharmacodynamics and Pharmacokinetics of New and Emerging DPP-4 Inhibitors<sup>21-24,a</sup>**

Agent	Ex-vivo DPP-4 Inhibition (%)		Metabolism	Elimination
	Maximum	24-hr Post-Dose		
<i>FDA-Approved Agents</i>				
Linagliptin	~80	70	~90% eliminated unchanged; exposure decreased by inducers of CYP 3A4 or P-gp	Biliary (>70% unchanged as parent drug), <6% via kidney
Saxagliptin	~80	~70	Hepatically metabolized to active metabolite via CYP 3A4/5	Renal (12-29% as parent drug, 21-52% as metabolite)
Sitagliptin	~97	80	Not appreciably metabolized	Renal (~79% unchanged as parent drug)
<i>Agent Pending FDA Approval</i>				
Alogliptin	~90	~75	Not appreciably metabolized	Renal (>70% unchanged as parent drug)

CYP = cytochrome; DPP = dipeptidyl peptidase; P-gp = p-glycoprotein  
<sup>a</sup>All agents are taken orally once daily.

**Question: What target A1c and therapeutic approach should be chosen for a high school principal who recently suffered a myocardial infarction and has newly-diagnosed type 2 diabetes, with A1c of 11.5% and a body mass index (BMI) of 29 kg/m<sup>2</sup>?**

The target A1c for this patient should be less than 7% (preferably <6.5%), which requires a reduction of at least 4.5%. Insulin therapy using a combination of basal and bolus doses is warranted initially, although therapy can be adjusted or changed once the A1c goal is achieved. Weight gain is a concern for this overweight patient (a BMI of 30 kg/m<sup>2</sup> or higher is considered obese), so therapies that promote weight

“

**Pharmacists should empower patients with type 2 diabetes to manage their disease by recommending the optimal pharmacotherapy that sets them up for success. The new and emerging GLP-1 agonists and DPP-4 inhibitors can play an important role in rational combination therapy for type 2 diabetes** ”

—Susan Cornell, Pharm.D., CDE, FAPhA, FAADE

gain (e.g., sulfonylureas, thiazolidinediones) are not ideal. To minimize weight gain, metformin could be added initially or later as the A1c is lowered to near or below 9% (i.e., as the magnitude of the reduction in A1c needed falls below 2%). A GLP-1 agonist or DPP-4 inhibitor also might be considered as the A1c approaches or falls below 9%.

## New Guidelines for Management of Hyperglycemia in Type 2 Diabetes Released in April

On April 19, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released a new joint position statement on the management of hyperglycemia in patients with type 2 diabetes. The new statement updates a consensus statement that was released by ADA and EASD in 2009, with recommendations that are less prescriptive and algorithmic than those in the 2009 statement because of a lack of comparative-effectiveness research. The following key points are made in the new statement:

- Glycemic goals and glucose-lowering therapies should be individualized based on the needs, preferences, and tolerances of the patient.
  - Diet, exercise, and education remain the cornerstone of treatment for type 2 diabetes.
  - Metformin remains the preferred first-line drug, unless there are contraindications to its use.
  - Adding one or two oral or injectable agents to provide combination therapy is reasonable, although side effects should be minimized if possible.
  - Many patients eventually require insulin therapy alone or in combination with other agents to maintain glycemic control.
  - When possible, therapeutic decision making should be a collaborative process, taking into consideration patient preferences, needs, and values.
  - Comprehensive cardiovascular risk reduction should be a major focus of antidiabetic therapy.
- Clinicians are encouraged to recognize the variable and progressive nature of type 2 diabetes, the specific role of each antidiabetic drug, patient- and disease-related factors that influence clinical decision making, and constraints imposed by age and comorbid conditions.

### Reference

Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 (online ahead of print April 19, 2012). Available at: <http://bit.ly/JSH7H1>

## Question: What other new drug therapies are in development for type 2 diabetes?

Sodium glucose cotransporter inhibitors (e.g., dapagliflozin, canagliflozin) that are administered orally and reduce the re-absorption of glucose in the proximal renal tubules have been developed.<sup>26,27</sup> In January 2012, FDA declined to approve dapagliflozin, the first agent in this new class of drugs, partly because of concerns about a possible link with breast and bladder cancer.<sup>28,29</sup> The agency requested additional clinical trial data.

Other new diabetes drugs in development include insulin degludec, an ultra-long-acting basal insulin that was injected subcutaneously once daily or three times a week in clinical studies.<sup>30</sup> A short-acting mealtime insulin product formulated as an inhalation powder in single-dose cartridges for use with a special inhaler is in late-stage clinical studies for the treatment of adults with type 1 or type 2 diabetes.

## References

1. Handelsman Y, Mechanick JL, Blonde L et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. *Endocr Pract.* 2011; 17(suppl 2):287-302. Available at: <http://www.aace.com/files/dm-guidelines-ccp.pdf>
2. Martin CL. Exploring the pharmacologic agents for treatment of type 2 diabetes. *The Diabetes Educator.* 2007; 33(suppl 1):6-13.
3. Rodbard HW, Jellinger PS, Davidson JA et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract.* 2009; 15:540-59.
4. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care.* 2012; 35(1 suppl):S11-63.
5. Nauck MA, Vilsboll T, Gallwitz B et al. Incretin-based therapies: viewpoints on the way to consensus. *Diabetes Care.* 2009; 32(suppl 2):S223-31.
6. Drucker DJ, Buse JB, Taylor K et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. *Lancet.* 2008; 372:1240-50.
7. Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1-5 studies. *Diabetes Obes Metab.* 2009; 11(suppl 3):26-34.
8. Ahren B. DPP-4 inhibitors. *Best Pract Res Clin Endocrinol Metab.* 2007; 21:517-33.
9. Buse JB, Drucker DJ, Taylor KL et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care.* 2010; 33:1255-61.
10. Gomis R, Espadero RM, Jones R et al. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2011; 13:653-61.
11. Byetta package insert. San Diego, CA: Amylin Pharmaceuticals, Inc.; December 2011.

## Additional ASHP Advantage Educational Activities

Visit the ASHP Advantage website to browse listings of convenient on-demand continuing education (CE) activities as well as publications, podcasts, and live webinars. More than 40 hours of free on-demand CE programming are available. Learn more and find a full listing of topics and activities at [www.asHPadvantage.com](http://www.asHPadvantage.com).



12. Victoza package insert. Princeton, NJ: Novo Nordisk, Inc; May 2011.
13. Gilbert MP, Pratley RE. Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus. *Am J Med.* 2009; 122(6 suppl):S11-24.
14. Bischoff LA, Jabbour SA, Miller JL. Exenatide once weekly in type 2 diabetes mellitus. *Expert Opin Pharmacother.* 2011; 12:1297-1303.
15. St Onge EL, Miller SA. Albiglutide: a new GLP-1 analog for the treatment of type 2 diabetes. *Expert Opin Biol Ther.* 2010; 10:801-6.
16. Umpierrez GE, Blevins T, Rosenstock J et al. The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study. *Diabetes Obes Metab.* 2011; 13:418-25.
17. Christensen M, Knop FK, Vilsboll T et al. Lixisenatide for type 2 diabetes mellitus. *Expert Opin Investig Drugs.* 2011; 20:549-57.
18. Bydureon package insert. San Diego, CA: Amylin Pharmaceuticals, Inc.; January 2012.
19. Ratner RE, Rosenstock J, Boka G et al. Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. *Diabet Med.* 2010; 27:1024-32.
20. Tzefos M, Harris K, Brackett A. Clinical efficacy and safety of once-weekly glucagon-like peptide-1 agonists in development for treatment of type 2 diabetes mellitus in adults. *Ann Pharmacother.* 2012; 46:68-78.
21. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab.* 2011; 13:7-18.
22. Tradjenta package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; July 2011.
23. Onglyza package insert. Princeton, NJ: Bristol-Myers Squibb; December 2011.
24. Januvia package insert. Whitehouse Station, NJ: Merck & Co., Inc; November 2011.
25. Glode A, Abdelghany S. Alogliptin: a dipeptidyl peptidase-IV inhibitor for the treatment of type 2 diabetes. *Formulary.* September 1, 2008. Available at: <http://bit.ly/JaglNj> (accessed 2012 Mar 8).
26. Strojek K, Yoon KH, Hrubá V et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2011; 13:928-38.
27. Devineni D, Morrow L, Hompesch M et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. *Diabetes Obes Metab.* 2012; 14:539-45.
28. Lowry F. Dapagliflozin declined by FDA. January 19, 2012. <http://www.medscape.com/viewarticle/757175> (accessed 2012 Feb 12).
29. U.S. Food and Drug Administration. FDA briefing document: NDA 202293 dapagliflozin tablets, 5 and 10 mg. Sponsor: Bristol-Myers Squibb. Advisory Committee Meeting. July 19, 2011. <http://1.usa.gov/IJNKfA>.
30. Zinman B, Fulcher G, Rao PV et al. Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. *Lancet.* 2011; 377:924-31.

**Planned and coordinated by ASHP Advantage and supported by an educational grant from Merck.**

