

Emerging Treatments for Type 2 Diabetes

Focus on Incretin Therapies



ASHP ADVANTAGE eNEWSLETTER

FEBRUARY 2014

New CE Offerings Available!

An educational initiative coordinated by ASHP Advantage is under way to provide health care professionals with timely education and resources on new and emerging treatment options for type 2 diabetes, including incretin-based therapies. Several new components of the initiative recently became available:

- **Live CE webinars**—Ask the Experts: A Controversial Dialogue in Diabetes— to be conducted on February 19 and March 13, 2014
- **Two 1-hour archived webinars** available on demand for which CE credit is available
 - **New and Emerging Treatment Options** in Type 2 Diabetes by Curtis Triplitt and Debbie Hinnen
 - **Clinical Case Studies** in the Management of Type 2 Diabetes: Interventions for Achieving Positive Patient Outcomes by Susan Cornell and Debbie Hinnen
- **A Guide to Emerging Treatments** for Type 2 Diabetes: Focus on Incretin Therapies, a monograph that can be downloaded and covers all aspects of incretin-based therapy, including rationale for development of the drugs and their pharmacology, dosing, adverse effects, and place in evidence-based treatment guidelines. One hour of CE credit is provided for successful completion of an online assessment test.



Ask the Experts: A Controversial Dialogue in Diabetes

Live CE webinar on February 19 and March 13, 2014 —
Register Now!

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- **A New Class of Drugs**—SGLT2 Inhibitors
- **New and Emerging Agents** for Type 2 Diabetes

Visit www.leadingdiabetescare.org for a complete listing of activities and resources.

A New Class of Drugs for Type 2 Diabetes—SGLT2 Inhibitors

In March 2013, canagliflozin, the first agent in a new class of drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitors, was approved by the Food and Drug Administration (FDA) for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.^{1,2} Dapagliflozin, another SGLT2 inhibitor, was approved by FDA for the same indication in January 2014.^{3,4} Other SGLT2 inhibitors (e.g., empagliflozin) are in the research and development pipeline.

The SGLT2 inhibitors interfere with the reabsorption of filtered glucose in the proximal renal tubule thereby increasing urinary glucose excretion, reducing blood glucose concentrations, and promoting weight loss.^{5,6} Canagliflozin has been studied as a stand-alone therapy and in combination with other type 2 diabetes therapies, including metformin, sulfonylureas, pioglitazone, and insulin.¹ Dapagliflozin has been studied as a stand-alone therapy and in combination with metformin, pioglitazone, glimepiride, sitagliptin, and insulin.³

The magnitude of the reductions in A1c achieved with canagliflozin and dapagliflozin are similar to those produced by other recently approved antidiabetic drugs.⁶ A relatively low risk of hypoglycemia is associated with the SGLT2 inhibitors.⁵ Urinary tract infections and female genital fungal infections are the most common adverse effects from these drugs. Modest reductions in systolic and diastolic blood pressure have been associated with the SGLT2 inhibitors.^{5,6} Postmarketing studies of the cardiovascular safety of these drugs (e.g., the Canagliflozin Cardiovascular Assessment Trial, commonly known as CANVAS, and Dapagliflozin Effect on Cardiovascular Events, referred to as DECLARE-TIMI-58) are in progress to comply

with FDA requirements for cardiovascular outcomes data for all new diabetes drugs.⁷ Results from CANVAS are expected in 2015.

Concerns have been raised about the risk for adverse events related to volume depletion and renal impairment (e.g., dizziness or fainting due to hypovolemia and dehydration) in patients taking SGLT2 inhibitors, especially older patients with renal dysfunction.^{5,6} The drugs should not be initiated in patients with severe renal impairment, including end-stage renal disease, or some patients with moderate renal impairment (patients with an estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m² for canagliflozin or eGFR <60 mL/min/1.73 m² for dapagliflozin).^{2,4} Possible links between dapagliflozin (but not canagliflozin) and bladder and breast cancer and liver injury were cause for concern in approval of the drug by FDA.⁶ The agency declined to approve the drug in 2011 largely because of these concerns. Early concerns about breast cancer and liver injury from dapagliflozin appear to have been dispelled by recent data.⁶ Postmarketing dapagliflozin safety studies will address the risk of bladder cancer and liver abnormalities among other safety endpoints.

Paradoxical increases in endogenous glucose production attributed at least in part to increased glucagon secretion recently were reported in two small studies of patients with type 2 diabetes receiving SGLT2 inhibitors (canagliflozin in one study and dapagliflozin in the other study) despite an overall decrease in fasting plasma glucose concentration.⁸⁻¹⁰ Because incretin-based therapies suppress glucagon secretion, a role for incretin-based therapies in combination with SGLT2 inhibitors has been suggested. Further research is needed.



Check out the Possibilities for Learning

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 30 hours of free on-demand CE programming are available.

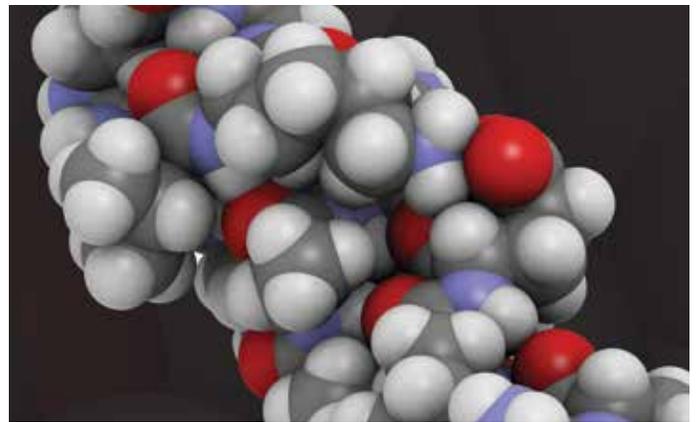
Learn more and find a full listing of topics and activities at www.ashpadvantage.com

New and Emerging Glucagon-Like Peptide-1 Receptor Agonists

Several long-acting glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., albiglutide, dulaglutide, semaglutide) are in clinical trials.¹¹ Albiglutide is nearing approval in Europe and under consideration by FDA, with action by FDA expected by April 15, 2014.¹² The drug is administered once weekly by subcutaneous (s.c.) injection. It may cause less nausea and vomiting than other long-acting GLP-1 receptor agonists because of limited access to the central nervous system.¹¹

Oral GLP-1 receptor agonists (e.g., liraglutide, dulaglutide, semaglutide) also are in development.¹³ A 26-week phase 2 clinical trial comparing the once-daily oral and once-weekly injectable forms of semaglutide began in December 2013.^{14,15} Results will be available in about 1 year. An oral route of administration would be advantageous for patients with type 2 diabetes who prefer to avoid injections.

An implantable s.c. pump delivery system for exenatide has been developed.¹¹ The pump is the size of a small match stick, and it can be inserted and removed in the physician office setting. Its use allows prompt achievement and continuous maintenance of steady-state plasma drug concentrations and rapid elimination of the drug after removing the pump if severe adverse effects occur. Preliminary data suggest that the pump is effective for providing glycemic control and weight loss and it is well tolerated, with favorable patient satisfaction scores. Use of the s.c. pump delivery system could overcome problems with patient nonadherence.



New Dual-Action Drug in Development

A new molecule with agonist activity at both GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptors has been developed for use by injection to treat patients with type 2 diabetes and obesity.^{16,17} Obesity is a common comorbid condition in patients with type 2 diabetes.¹⁸ The incretins GLP-1 and GIP are gastrointestinal (GI) hormones that promote pancreatic secretion of insulin in response to increases in plasma glucose concentrations after meals. Suppression of appetite also is associated with GLP-1. Nausea and vomiting often limit the use of GLP-1 receptor agonists. Researchers hope that targeting receptors for GLP-1 and GIP will provide synergy with enhanced potency for reducing blood glucose concentrations while minimizing the GI adverse effects that can limit the use of GLP-1 receptor agonists. Results of a 6-week study of 53 obese patients with type 2 diabetes are promising, but additional clinical research using the drug for longer periods in larger numbers of patients is needed.



Visit the Resource Center at www.leadingdiabetescare.org

- Quick links to diabetes guidelines and treatment algorithms
- Tools for clinicians who manage patients with type 2 diabetes
- Diabetes educational materials

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Planned and coordinated by ASHP Advantage.

This activity is supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc., which was made possible, in part, through collaboration with Eli Lilly, and an independent medical education grant from Bristol-Myers Squibb and AstraZeneca LP.

