Emerging Treatments for Type 2 Diabetes

Focus on Incretin Therapies

ASHP ADVANTAGE eNEWSLETTER DECEMBER 2013

Interprofessional Educational Initiative

Incretin agents—glucagon-like peptide-1 (GLP-1) receptor agonists and inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme that degrades GLP-1—are among the new and emerging treatment options for type 2 diabetes addressed in an educational initiative coordinated by ASHP Advantage for health care professionals. This e-Newsletter is part of the initiative, which is designed to help pharmacists, nurses, nurse practitioners, and diabetes educators learn practical strategies for improving patient outcomes through collaborative, team-based diabetes care. Other featured activities of the initiative include

- **Live CE webinars** on new and emerging treatments for type 2 diabetes, particularly new and existing incretin agents, with clinical case studies in the management of the disease and answers to questions from webinar participants
- **On-demand CE activities** developed from archived versions of the live CE webinars
- **A discussion guide** with a detailed discussion of the characteristics and place in therapy of incretin agents
- **Podcast interviews** of faculty to provide insight about therapeutic issues in diabetes patient care
- **An online resource center** with useful information for health care providers caring for patients with type 2 diabetes.

The educational activities are available free of charge. Membership in ASHP is not required. Visit **www.leadingdiabetescare.org** for a complete listing of activities and resources and to sign up for email updates about learning opportunities.

In this issue:

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Recent Type 2 Diabetes Treatment Trends

The prevalence and economic impact of diabetes are increasing in the United States. The estimated total economic cost of diagnosed diabetes in 2012 was $245 billion, representing a 41% increase since 2007.[1] In 2012, approximately 7% of the U.S. population—more than 22.3 million Americans—were diagnosed with diabetes.[1] By 2050 as many as one in three American adults are expected to have diabetes.[2]

Prescription medications account for a substantial portion of the costs of diabetes.[1] GLP-1 receptor agonists and DPP-4 inhibitors lack some of the disadvantages of older antidiabetic therapies (e.g., weight gain and hypoglycemic effects from sulfonylureas and insulin, heart failure and weight gain from thiazolidinediones). Weight loss has been associated with GLP-1 agonists, and DPP-4 inhibitors are weight neutral. In guidelines for the management of type 2 diabetes from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes, incretin therapies are part of some of the two- and three-drug combinations recommended for patients with inadequate glycemic control from first-line therapy using metformin plus lifestyle modification.[3]

The results of an analysis of trends in diabetes medication prescribing by office-based physicians for ambulatory adults 35 years of age or older in the United States between 1997 and 2012 recently were released.[4] Treatment visit was defined as a patient encounter during which one or more drug therapies were prescribed.

Sulfonylureas were widely used in 1997, when they accounted for 61% of treatment visits, but these drugs have fallen out of favor since then. They were used in 22% of treatment visits in 2012. Use of the biguanide metformin has increased steadily over that time frame from 24% (1997) to 53% (2012) of treatment visits, reflecting recognition of the role of the drug as the cornerstone of treatment for type 2 diabetes. The use of metformin did not increase substantially after 2010 (i.e., a plateau in use of the drug was reached).

The use of thiazolidinediones (i.e., glitazones) increased between 1997, when they first became available, and 2005, when they were used in 41% of treatment visits. Recognition of the cardiovascular risks associated with rosiglitazone caused a decrease in use of this drug class to 16% of treatment visits in 2012, when almost all use involved pioglitazone.

The use of insulin as a drug class has not changed substantially between 1997 and 2012, when it accounted for roughly one in four treatment visits. However, marked changes in the type of insulin used have been observed since the introduction of new insulin analogs, especially the long-acting insulin glargine and short-acting insulin aspart in 2000. The use of long-acting insulin increased from less than 1% of treatment visits in 1997 to nearly 18% of treatment visits in 2012. The use of short-acting insulin increased over the same period, although not to the same extent. By contrast, the use of regular and intermediate insulins fell below 5% in 2012.

The use of DPP-4 inhibitors has increased steadily since these oral agents were introduced in 2006 to 21% of treatment visits in 2012. The use of GLP-1 agonists, which are administered by subcutaneous injection, also increased since their 2005 introduction, although at a less rapid rate and to a lesser extent, accounting for 4% of treatment visits in 2012.

The percentage of visits for a single antidiabetic agent (i.e., monotherapy) decreased from 54% in 1997 to 35% in 2012, while the percentage of visits for two or more agents (i.e., combination therapy) increased from 41% to 58% in the same period. In 2012, the most common monotherapy was metformin (53%) followed by insulins (15%), sulfonylureas (12%), DPP-4 inhibitors (10%), GLP-1 agonists (4%), and thiazolidinediones (3%). The most common combination therapies in 2012 were metformin plus a sulfonylurea (31%) and metformin plus a DPP-4 inhibitor (20%). Nearly three fourths of all DPP-4 inhibitor use was as part of combination therapy. The average number of agents used per treatment visit increased by 27% from 1.32 in 1997 to 1.68 in 2012, reflecting a progressively greater emphasis on combination therapy over the 15-year period.

Diabetes drug expenditures increased by 61% between 2008 and 2012. The increased use of insulin glargine and DPP-4 inhibitors were the largest contributors to this increase.

These trends in diabetes medication use may reflect an increased understanding of the etiology of diabetes as a disease involving multiple organ defects that often requires combination drug therapy and recognition of the role of incretins in the pathogenesis of type 2 disease (i.e., diminished GLP-1 secretion in patients with longstanding type 2 diabetes). Published evidence-based guidelines have evolved to reflect the increased complexity of treatment for type 2 diabetes.

Incretin Agent Use in Hospitalized Patients with Type 2 Diabetes

The increasingly wide use of incretin therapies has raised questions about the use of these agents in patients with type 2 diabetes who are admitted to the hospital for acute illness or surgery. Treatment guidelines from the Endocrine Society, American Association of Clinical Endocrinologists, ADA, and American College of Endocrinology recommend against the use of noninsulin therapies, including incretin agents, for these patient populations because contraindications to use of the drugs often are present at the time of admission or develop during hospitalization.[5] These contraindications include sepsis, renal failure, pancreatic disorders, use of intravenous (IV) contrast dye for diagnostic procedures, and restrictions on oral dietary and medication intake (i.e., NPO status).[5] Although selected patients who received noninsulin therapy in the outpatient setting may continue it in the inpatient setting if they are clinically stable, anticipate eating meals at regular intervals, and have no contraindications, the use of noninsulin agents in the inpatient setting is inappropriate for most patients.[5,6] Concerns associated with noninsulin therapy in inpatients depend on the drug (Table 1). The onset of the blood glucose-lowering effect of most oral agents is not sufficiently fast to meet the rapidly changing needs of inpatients for glycemic control. Noninsulin therapy should be discontinued at the time of admission of most patients with type 2 diabetes and acute illness, and insulin therapy should be used instead.[5] Noninsulin therapy also should be discontinued for patients with diabetes who are admitted for surgery, and insulin therapy should be initiated if hyperglycemia develops during the perioperative period in these patients.[5] Patients who received insulin therapy on an outpatient basis should receive a subcutaneous (SC) insulin regimen while hospitalized.[5] The Endocrine Society recommends that health systems incorporate alerts into their systems (e.g., computerized prescriber order entry) to identify patients with type 2 diabetes who have been receiving noninsulin therapy on an outpatient basis and have contraindications to its continued use at the time of hospital admission.[5]

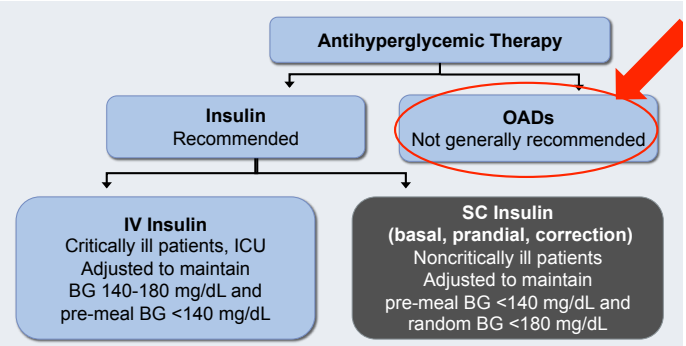
Table 1. Key Concerns Associated with Commonly Used Noninsulin Therapies in Hospitalized Patients[5,7]

Drug Class or Drug	Concerns
Biguanide (metformin)	Should not use in patients receiving IV contrast dye, undergoing surgery, or with decompensated congestive heart failure, renal insufficiency, hypoperfusion, chronic pulmonary disease, or at risk of lactic acidosis
DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin)	Limited usefulness for patients with low or no oral dietary intake because act primarily on PPG
GLP-1 agonists (exenatide, liraglutide)	Limited usefulness for patients with low or no oral dietary intake because short-acting GLP-1 agonists act primarily on PPG (long-acting GLP-1 agonists act on both FPG and PPG). Also, both short- and long-acting GLP-1 agonists have adverse GI effects such as nausea.
Sulfonylureas	Risk of severe, prolonged hypoglycemia, especially in patients who are elderly or with renal impairment or poor nutritional intake
Thiazolidinedione (pioglitazone)	Prolonged time to achieve full hypoglycemic effect Should not use in patients with congestive heart failure, hemodynamic instability, or evidence of hepatic dysfunction

DPP = dipeptidyl peptidase, GLP = glucagon-like peptide; IV = intravenous; PPG = postprandial plasma glucose

The glycemic goals and insulin regimen used in hospitalized patients depend on patient clinical status (Figure 1). In most critically-ill patients (e.g., patients in intensive care units), IV insulin should be used to maintain a plasma glucose concentration of 140–180 mg/dL, with premeal levels less than 140 mg/dL.[6] Scheduled SC insulin, with basal, prandial (i.e., nutritional), and correction (supplemental) components, is preferred for providing glycemic control in noncritically-ill hospitalized patients.[6] A long-acting insulin (e.g., insulin glargine or detemir) should be used for the basal component. A rapid-acting insulin (e.g., insulin aspart, lispro, or glulisine) or short-acting insulin (i.e., regular) may be used for prandial (premeal) and correction doses.[5] A premeal plasma glucose concentration less than 140 mg/dL and random blood glucose concentrations less than 180 mg/dL are sought for most noncritically ill inpatients.[5,6] More stringent glycemic goals may be used for patients who are stable and had tight glycemic control without hypoglycemia prior to hospitalization.[5,6] Less stringent goals (e.g., random blood glucose <200 mg/dL) might be more appropriate for patients who are terminally ill or have serious comorbid conditions, a limited life expectancy, or severe hypoglycemia.[5,6] The prolonged use of sliding scale regular insulin alone is not recommended because it often results in large glycemic excursions (i.e., hypoglycemia or hyperglycemia).[5,6,8] Frequent assessment of clinical status and the use of clinical judgment are needed in managing hyperglycemia using insulin therapy in hospitalized patients.

Figure 1. Management of Type 2 Diabetes in the Hospital Setting



OAD = oral antidiabetic; IV = intravenous; SC = subcutaneous; ACE = American College of Endocrinology; ADA = American Diabetes Association.
ACE/ADA Task Force on Inpatient Diabetes. *Diabetes Care.* 2006 & 2009. *Diabetes Care.* 2009;31(Suppl 1):S1-S110. Umpierrez GE et al. *J Clin Endocrinol Metab.* 2012;97(1):16-38.

Planning for hospital discharge of patients with type 2 diabetes should begin at the time of admission.[6] Patients who had good glycemic control using noninsulin therapy prior to hospitalization may be discharged with the same regimen unless there are contraindications to use of the regimen.[5] If insulin therapy will be required after discharge of a patient who did not use it prior to admission, education should be provided about proper administration technique for the patient or his or her caregiver.

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For complete information about educational activities that are part of this initiative, visit www.leadingdiabetescare.org. There is no charge for the activities, and ASHP membership is not required.

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