

# Emerging Treatments for Type 2 Diabetes

## Focus on Incretin Therapies

ASHP ADVANTAGE eNEWSLETTER

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## Improving Outcomes through Collaborative, Team-based Care

ASHP Advantage is coordinating an educational initiative designed to provide health care professionals with timely education and resources on new and emerging treatment options in type 2 diabetes, including incretin-based therapies. Pharmacists, nurses, nurse practitioners, and diabetes educators will learn practical strategies for improving patient outcomes through collaborative, team-based diabetes care. Featured activities 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
- **E-Newsletters** with the latest science and emerging information on the use of incretin therapy in type 2 diabetes
- **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](http://www.leadingdiabetescare.org) for a complete listing of activities and resources and to sign up for email updates about learning opportunities.



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## Why Focus on Type 2 Diabetes and Incretin-Based Therapy?

Diabetes is a common disease that affects an estimated 25.8 million Americans or 8.3% of the U.S. population.<sup>1</sup> It is a major cause of heart disease and stroke and the leading cause of kidney failure, non-traumatic lower limb amputation, and new cases of blindness among American adults. Diabetes is the seventh leading cause of death in the United States.

The total annual economic cost of diabetes has risen 40% from \$174 billion in 2007 to \$245 billion in 2012.<sup>2</sup> The 2012 figure includes \$176 billion for direct medical expenditures (hospital and emergency care, medications, and office visits) and \$69 billion for indirect costs (work absenteeism, reduced productivity, and unemployment).<sup>3</sup>

The high morbidity and mortality from type 2 diabetes have spurred research to further elucidate the pathogenesis of the disease and identify new therapeutic modalities to improve clinical outcomes. Incretins (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide) are gastrointestinal hormones that promote pancreatic secretion of insulin after the ingestion of food. A diminished incretin effect in response to meals has been identified in patients with type 2 diabetes.<sup>4</sup> Recognition of this pathophysiologic mechanism in type 2 diabetes led to the development of incretin analogs (also called GLP-1 receptor agonists) and inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme that degrades incretins.<sup>5</sup>

Current evidence-based guidelines for the treatment of type 2 diabetes from the American Diabetes Association and the European Association for the Study of Diabetes call for dual drug therapy if metformin monotherapy (the initial drug therapy of first choice) is not successful in achieving the target A1c within 3 months.<sup>6</sup> Incretin therapy is among the options for use in combination with metformin. Other options may be problematic because of adverse effects—hypoglycemia and weight gain from sulfonylureas and insulin, and weight gain, fluid retention leading to edema and heart failure, and increased risk of bone fractures from thiazolidinediones.

Although incretin therapies are not without adverse effects (e.g., nausea from GLP-1 agonists), they may play an important role in managing type 2 diabetes. Several incretin therapies are available in the United States, including the DPP-4 inhibitors sitagliptin, saxagliptin, linagliptin, and alogliptin and the GLP-1 receptor agonists exenatide and liraglutide. Additional agents (e.g., albiglutide and dulaglutide) are in development. Differences among these agents may influence selection of drug therapy. Research indicates that GLP-1 also modulates blood pressure, heart rate, vascular tone, and myocardial contractility, with the potential for cardiovascular benefits independent of glycemic control.<sup>7</sup> Two recent cardiovascular outcomes trials with the DPP-4 inhibitors, saxagliptin and alogliptin, were neutral.<sup>8,9</sup> To date, no cardiovascular outcomes trials with GLP-1 receptor agonists have been completed.



### 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](http://www.ashpadvantage.com)

## Addressing Concerns about Pancreatitis and Pancreatic Cancer

The Food and Drug Administration (FDA) is investigating postmarketing reports of acute pancreatitis, including fatal and serious nonfatal cases, associated with the use of the incretins exenatide and sitagliptin.<sup>10,11</sup> These two agents have been the focus of these investigations primarily because they have been available for longer than other incretin agents.<sup>12</sup> Warnings and precautions about pancreatitis appear in the prescribing information for all incretin agents, since cases of pancreatitis have been reported with each of them. The safety concerns are the subject of considerable controversy, because a biological mechanism for pancreatitis in patients receiving incretin therapies has not been identified.<sup>11,13,14</sup> Most large database studies with incretins have not found a significant risk of pancreatitis compared with other antihyperglycemic therapies.<sup>15-17</sup> In contrast, results of a population-based case-control study of a large administrative database of American adults with type 2 diabetes were released.<sup>18</sup> Treatment with exenatide or sitagliptin was associated with increased odds of hospitalization for acute pancreatitis compared with nonuse. In a joint response to publication of these study findings, the American Association of Clinical Endocrinologists and American Diabetes Association (ADA) noted that the results do not provide the basis for changing treatment in people with diabetes because of the retrospective nature of the study and small excess risk for hospitalization for acute pancreatitis (two additional cases per 100 patients over a 3-year period) associated with incretin therapy.<sup>19</sup>

Chronic pancreatitis and diabetes mellitus are among the risk factors for pancreatic ductal adenocarcinoma (other risk factors include family history, smoking, and obesity).<sup>20</sup> The incidence of this malignancy has been increasing in the United States in part because of recent increases in type 2 diabetes. Epidemiologic data suggest that the risk for developing pancreatic cancer varies among different antidiabetic therapies, with an increased risk from incretin therapies and a protective effect from metformin.<sup>21</sup> In an April 2013 analysis of cases of pancreatitis and pancreatic cancer in patients receiving incretin therapies reported to the Institute for Safe Medication Practices, the odds were increased from all currently available incretin therapies (except alogliptin, which was approved by FDA only recently in January 2013) compared with diabetes drug controls.<sup>22</sup> More important, these adverse event data lack the robustness of clinical trial data and suggest the need for further investigation.

Pancreatic cancer, pancreatitis, and diabetes are interrelated in a complex manner that makes attributing one illness solely to another or its treatment problematic. Pancreatic cancer causes pancreatitis, which can cause diabetes.<sup>23</sup> Chronic pancreatitis can cause cancer. Pancreatic cancer could be attributed mistakenly to antidiabetic treatment in patients whose cancer arose from other causes. An estimated 82% increase in risk for pancreatic cancer is associated with diabetes independent of antidiabetic therapy.<sup>12</sup>

A 2-day workshop on pancreatitis-diabetes-pancreatic cancer was convened in Bethesda, Maryland, by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute on June 12 and 13, 2013.<sup>24</sup> Participants included representatives from the pharmaceutical industry, FDA, and other government agencies as well as epidemiologists, clinicians, and academic faculty. Exploring the known and suspected mechanisms for the increased risk for pancreatic cancer associated with chronic pancreatitis and diabetes mellitus and reviewing the effects of antidiabetic therapy on the development of this malignancy were among the goals of this workshop. The consensus of workshop participants was that there probably is no increased risk for pancreatic cancer from incretin therapies, although the possible link between incretin therapies, pancreatitis, and pancreatic cancer requires further investigation and long-term data because of the complexity of the diseases.<sup>23</sup> The available evidence does not suggest a need for current or prospective users to discontinue or avoid GLP-1 mimetics or DPP-4 inhibitors.<sup>25</sup>

In July 2013, the European Medicines Agency released the results of its own analysis of the safety of incretin therapies. The group concluded that recent concerns over an increased risk for pancreatic adverse events from these agents are not confirmed by currently available data.<sup>26</sup>

The results of nine ongoing prospective, randomized, controlled clinical trials of incretin therapies involving more than 65,000 patients should provide additional information about the risks and benefits from these agents.<sup>19</sup> The ADA called for pharmaceutical companies involved in the development or marketing of incretin therapies to make patient-level data on their products available for an independent review so that the contribution of these agents to pancreatitis or pancreatic cancer can be ascertained.<sup>27</sup>

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

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