The Changing Landscape of Type 2 Diabetes: The Role of Incretin-Based Therapies in Managed Care Outcomes

Curtis Triplitt, PharmD, CDE
Janet B. McGill, MD
Daniel Porte Jr., MD
Christopher S. Conner, PharmD
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Purpose
Provide a review of incretin physiology and the latest clinical data on GLP-1 mimetics and DPP-4 inhibitors. From this foundation, practical issues of disease management, including therapeutic inertia, updates on clinical recommendations, and evaluation of the best fit for incretin-based therapies in current treatment paradigms will be considered.

Target Audience
Managed care pharmacists, pharmacy directors, and medical directors involved in caring for the growing population of individuals with type 2 diabetes

Learning Objectives
Upon completion of this activity, attendees will be better able to
1. identify the impact of clinical inertia and recently released clinical practice recommendations on the management of type 2 diabetes;
2. define the physiologic actions of the incretins GIP and GLP-1 on β-cell function and glucose homeostasis;
3. interpret the latest clinical data available on new incretin-based therapies, including GLP-1 analogues/agonists and DPP-4 inhibitors, and
4. evaluate the anticipated place for incretin-based therapies in current treatment paradigms.

This supplement was funded by an unrestricted educational grant from Novartis Pharmaceuticals Corporation and was jointly sponsored by Medical Education Resources (MER) and Consensus Medical Communications (CMC).

The article in this supplement is based on the proceedings of a symposium “The Changing Landscape of Type 2 Diabetes: The Role of Incretin-Based Therapies in Managed Care Outcomes” held April 11, 2007, in San Diego, California, which was also supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation and jointly sponsored by MER and CMC.

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ABSTRACT

BACKGROUND: The prevalence of diabetes is growing in the United States and, for many patients, blood glucose continues to be poorly managed. Significantly, more than half of people with type 2 diabetes mellitus (T2DM) have hemoglobin A1Cs greater than 7%. Several factors contribute to the failure to achieve treatment goals, including clinical inertia (the failure to initiate or advance therapy in a patient who is not at the evidence-based therapeutic goal) and failure to address all components of disease pathophysiology. Newer classes of antihyperglycemic agents, the incretin-based therapies, have the potential to improve goal achievement.

OBJECTIVE: To review incretin physiology and the latest clinical data on glucagon-like peptide-1 (GLP-1) mimetics and dipeptidyl peptidase-IV (DPP-4) inhibitors and to use this as a foundation to discuss the practical issues of disease management, including clinical inertia, clinical recommendations, and evaluation of the best fit for incretin-based therapies in current treatment paradigms.

SUMMARY: Clinical inertia is an important contributing factor to T2DM treatment failure and may be improved through more specific diagnosis, more complete patient education, and an emphasis on earlier and more aggressive therapy in goal-oriented fashion. Based largely on the underlying pathophysiology of T2DM, newer ACE/AACE guidelines have been developed to facilitate this more aggressive approach. The incretin-based therapies can favorably impact some underlying elements in T2DM pathophysiology, including glucagon hypersecretion, rapid gastric emptying, postprandial hyperglycemia, and, possibly, chronic β-cell dysfunction. When incorporated early into a long-term, treat-to-target management plan, incretin-based therapies have the potential to reduce the prevalence of treatment failure in T2DM and may positively impact disease progression.

CONCLUSIONS: Clinicians need to recognize and address the scope and impact of clinical inertia on T2DM patient outcomes. Better use of conventional treatment options and/or consideration of newer incretin-based therapies can contribute to improvements in patient health.

J Manag Care Pharm. 2007;13(9)(suppl S-c):S2-S16

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Authors

CURTIS TRIPLITT, PharmD, CDE, is a clinical assistant professor of medicine, Texas Diabetes Institute, and a clinical assistant professor of pharmacy, University of Texas Health Science Center, San Antonio, Texas; JANET B. MCGILL, MD, is an associate professor of medicine, Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, and an attending consultant, Barnes-Jewish Hospital, St. Louis, Missouri; DANIEL PORTE JR., MD, is a professor of medicine, University of California–San Diego, and a staff physician, VA San Diego Healthcare System, California; and CHRISTOPHER S. CONNER, PharmD, is a clinical pharmacist and director emeritus of Rocky Mountain Drug Consultation Center, Lakewood, Colorado.

AUTHOR CORRESPONDENCE: Curtis Triplitt, PharmD, CDE, Clinical Assistant Professor of Medicine, Texas Diabetes Institute, 701 S. Zaragosa Street (MS 10-5), San Antonio, TX 78207. Tel.: 210.358.7544; Fax: 210.358.7235; E-mail: Curtis.Triplitt@uhs-sa.com

Type 2 diabetes mellitus (T2DM), which represents 90%-95% of all cases of diagnosed diabetes, is increasing in the United States. More than 18 million individuals are affected, compared with approximately 10 million a decade ago.1,2 Contributing to this increased prevalence is the problem of obesity, which is a major risk factor for T2DM development and has, in itself, become an epidemic.3,4

Microvascular complications, including retinopathy and neuropathy, as well as cardiovascular (CV) morbidities related to T2DM, such as coronary heart disease, myocardial infarction, and stroke, are seen in almost 60% of cases.5 The economic burden of T2DM in the United States is enormous. An estimated $22.9 billion in direct costs is spent annually on managing T2DM complications alone, and total annual health-related expenditures of T2DM and its complications amount to $57.1 billion, with out-of-pocket expenses totaling more than $8 billion.6 These figures underestimate total costs for T2DM because they do not account for indirect costs such as disability and loss of work days.

Because health care costs are approximately 3-fold higher in patients with T2DM compared with those without,2 ways to improve management and reduce the frequency of complications are of high interest to managed care organizations. Studies have shown that glycemic control in people with diabetes is cost-effective.3 A sustained reduction in rates of microvascular and neuropathic complications, and possibly macrovascular CV events, can be achieved in T2DM patients by intensive glycemic control, which is best reflected by hemoglobin A1C (AIC) levels.8 Reduction of A1C levels to 7% or lower has correlated with the best clinical trial-based outcomes and helped form the basis for the current recommendation of the American Diabetes Association (ADA) to maintain AIC <7%.9 An even lower AIC target (≤6.5%) is advocated by the American College of Endocrinologists (ACE) and the American Association of Clinical Endocrinologists (AACE).2

However, data from the National Health and Nutrition Examination Survey III (NHANES III) suggest that AIC goal attainment is suboptimal. Sixty-three percent of adult patients fail to meet the <7% AIC target, and approximately 20% have AICs >9%. Furthermore, 93% fail to achieve combined goals for AIC, blood pressure, and cholesterol.7 More recently, data released by AACE suggest similar findings—67% of Americans with T2DM are not achieving and/or maintaining the AACE goal of ≤6.5%.2

Failure to Achieve Treatment Goals

Many factors contribute to the failure to achieve recommended goals. A key first step in reaching treatment targets for T2DM is the understanding that clinical inertia—the failure to initiate
or advance therapy in a patient who is not at the evidence-based therapeutic goal—may be troublesome in many aspects of patient care. Adoption of a more aggressive treat-to-target approach rather than the standard practice of waiting for treatment failure may help to achieve goals.

Clinical Inertia

A common problem, clinical inertia represents a primary cause of poor glycemic control in T2DM.9,10 The concept of clinical inertia is illustrated in a large, prospective study by Brown et al. involving patients who were members of Kaiser Permanente Northwest.10 The first and best A1C values achieved were assessed for 7,000 complete courses of treatment with stepwise nondrug therapy, sulfonylurea monotherapy, metformin monotherapy, and combination therapy for an 8-year period (1994-2002). Figure 1 shows subjects never achieved ADA- or AACE-recommended A1C levels on metformin or sulfonylurea monotherapy. Best mean A1C levels reached 7.7% and 7.1%, respectively. However, A1C levels rose to 8.8% and 9.1% (on average) in these respective groups before a change in therapy was initiated. The time required until new or additional treatment was started (with A1Cs above goal) ranged from 2 to 3 years. Clinical inertia in T2DM is evident in other studies,9,11-13 one of which documented that less than half of patients with A1Cs > 8% received therapy intensification or modification, regardless of physician specialty.13

Considering the progressive decline in pancreatic β-cell function in T2DM,14-16 overcoming clinical inertia is essential to slow or prevent the onset of complications and improve overall outcomes. The causes of clinical inertia are multifactorial. Primary responsibility lies with the provider but can be greatly impacted by other interrelated facets: the system of care, the patient, and available treatments.

The Provider

The central point of clinical inertia is the failure to intensify therapy when needed. Reasons for this may include a provider’s lack of certainty regarding the appropriate A1C target, lack of “treat-to-target” training, or lack of adherence to available guidelines.12 Providers may also overestimate their adherence to guidelines,13 or conversely, believe there is no consensus on therapeutic goals. Providers may not attempt to achieve goals, citing risks for hypoglycemia or other adverse effects, such as weight gain. A posture of hopelessness due to late diagnosis can be contributory. In fact, T2DM is usually diagnosed 4 to 7 years after its onset,1 when both macrovascular and microvascular complications have already begun to develop. It is known that β-cell dysfunction, and thus impaired insulin secretion, can occur up to 10 years prior to diagnosis, with loss of up to 50% of secretory function when T2DM is first recognized.17 Knowledge of this, and that β-cell dysfunction is progressive,18-20 may render many clinicians less than zealous about therapeutic options. Hence, clinical inertia may occur.

Major recent findings from NHANES III and NHANES 99-00 are that rates of glycemic control and other factors such as demographic distribution of the disease have changed substantially in recent years. These data suggest that antihyperglycemic agents are underused in T2DM patients, despite the availability of additional therapeutic options to improve glycemic control.20 This may be related to the reluctance of physicians or patients to insist on implementation of new therapies. Instead, inadequate therapy is continued.

The System

The clinical steps in diagnosing and managing patients with T2DM constitute a system, whether in an outpatient clinic, primary care or specialist office setting, pharmacy service, or specialized diabetes care center or clinic. In this system of care, needs of the T2DM patient must be a priority, or clinical inertia will occur.

Lack of sufficient time to address patient problems is one system factor that may lead to clinical inertia. In the typical office of a busy internist, for example, prespecified T2DM patient-visit times are important in order to shift focus from a time-rushed practice to the patient’s clinical management. Laboratory data must be available prior to seeing the patient; this facilitates onward movement and obviates having to reschedule the appointment.
Compounding the system barriers within the practice setting, T2DM is often treated within the acute-care model, meaning one patient problem is solved on one visit, or complications are treated as they arise. However, it is important to consider T2DM within a chronic-care model,19 where thinking is shifted to preventing complications, which in turn begets a closer look at maintaining A1C levels at or below goal and minimizing clinical inertia.

The Patient

Patients can positively or negatively impact clinical inertia. Those who take charge of their own health will likely fare much better. However, Americans in general tend to have unhealthy lifestyles,20 and many people with diabetes reside in this category. Most do not adhere to the dietary goals that may improve glycemic control,21 and many are obese; both situations fuel micro- and macrovascular risk.6 Lack of adherence to prescribed medications is common among T2DM patients.22

Those who assume responsibility for the management of their T2DM and know the importance of maintaining goal A1Cs may be more likely to practice healthy lifestyles, accept the “intrusion” of treatment on their lifestyles, and follow the regimen of prescribed medications. They also are more likely to raise the issue of intensification of therapy with their provider if their blood glucose readings begin to deteriorate or if A1C levels are above goal. In this respect, the patient can prompt the change in treatment, lessening clinical inertia.

Results of a recent study suggest that good self-management alone can reduce clinical inertia, with no prompting necessary. In a large cohort of insured T2DM patients, medication adherence (as a reflection of proper self-management practices) was assessed in relation to intensification of therapy for a first elevated A1C value after starting therapy. Those patients in the highest quartile of medication adherence were significantly more likely to have their regimens intensified than were those in the lower quartile of adherence.8 The reflection of good self-care seems to impart more willingness on the part of the care provider to implement therapy adjustments.

Patient education is paramount to stress the importance of self-care, reasons for medications, and consequences of non-adherence. All patients should fully understand that maintaining goal A1C levels can lower the risk of negative, long-term outcomes.

In addition to these systematic issues affecting optimal patient care, antidiabetic treatments themselves can compound the challenges of clinical inertia.

Available Treatments

Monotherapy with conventional oral antidiabetic agents often fails,17,23 consistent with the inability to alter the progressive decline in β-cell function in T2DM. In the United Kingdom Prospective Diabetes Study 49 (UKPDS 49), newly diagnosed T2DM patients (N=4075) were treated with diet alone, metformin, insulin, or a sulfonylurea and were followed for 9 years. Although all monotherapy regimens were initially effective in increasing the number of patients achieving A1C levels of <7% compared with patients achieving those levels on diet alone (by up to 3-fold), this increase waned with time. By 3 years, only about half of monotherapy patients could maintain this goal, and at 9 years, the proportion decreased to 25%.23 These findings indicate that monotherapy is frequently insufficient in sustaining goal A1C levels over time.

In a more recent monotherapy study, A Diabetes Outcome Progression Trial (ADOPT), the thiazolidinedione (TZD) rosiglitazone was shown to significantly prolong the time to treatment failure, defined as fasting plasma glucose >180 mg per dL, compared with metformin or glyburide in recently diagnosed T2DM patients.24 The cumulative incidence of failure at 5 years (Kaplan-Meier analysis) with these respective agents was 15%, 21%, and 34%. However, in an analysis of A1C data, the mean A1C was only 0.13% less in the rosiglitazone group compared with the metformin group at 4 years, and rosiglitazone did not prevent A1C levels from increasing over time (Figure 2). A1C increases over this time were greater in the glyburide group; mean A1C was 0.42% lower in the rosiglitazone group at 4 years. Although the TZDs may possess some β-cell-preserving effects,25,26 ADOPT suggests that monotherapy with rosiglitazone is insufficient to fully arrest long-term β-cell decline.26

More so than between-agent efficacy differences, the thrust of UKPDS and ADOPT data is that conventional monotherapies are not capable of sustaining target A1C levels for prolonged periods. Thus, the time-honored stepwise management protocol in T2DM, with monotherapy, then monotherapy dose increases,
then combination therapy when single agents fail, may be contributing to clinical inertia. Providers must move away from this and toward goal-oriented therapeutic interventions if long-term glycemic control and an attendant reduction in complications are to be realized.

Shifting Away From Clinical Inertia: Goal-Oriented Therapy
A goal-oriented treatment approach is intended to help patients reach glycemic targets expeditiously and maintain them, shifting the emphasis from monotherapy to early combination therapy, which is often needed for long-term glycemic control. The rationale is that most patients will eventually require a second drug anyway, and combination therapy provides greater A1C reductions and brings more patients to goal than does monotherapy. Adding a second drug can also be preferable to increasing the dose of monotherapy in patients with persistent hyperglycemia, particularly for the sulfonylureas, in which 70%-80% of maximum efficacy is seen at about half of the maximum recommended dose. This emerging shift is most closely embodied in newer guidelines and algorithms by ACE/AACE.

The “Road Map” established by ACE/AACE targets postprandial and fasting plasma glucose levels based on initial A1C values, and combination therapy is advocated as initial therapy for A1C levels >7%. (See road map at www.aace.com/pub/roadmap/index.php.) It suggests additional intensification strategies to reduce A1Cs to goal, if goal is not achieved after a short trial of recommended interventions. It should be noted that earlier use of insulin is recommended to control A1C levels. Not to be neglected are measures to control blood pressure, lipids, and body weight; controlling all of these is significant to reduce CV complications.

The ACE/AACE goal-oriented (or treat-to-target) approach employs a different method of clinical thinking than traditional practices that may lead to clinical inertia. For example, if A1C reaches 6.5%, clinicians should consider the addition of another agent—a sharp contrast to the slow-moving, wait-and-see reaches 6.5%, clinicians should consider the addition of another practices that may lead to clinical inertia. For example, if A1C employs a different method of clinical thinking than traditional complications.

Summary: Overcoming Clinical Inertia
With knowledge of the underlying pathophysiology of T2DM and its progressive nature, clinicians can better understand the rationale for newer guidelines and the applicability of newer modalities in the management of T2DM.

Providers’ improved focus on early diagnosis, greater patient education, earlier combination therapy, and intensification of therapy to attain established goals may help to overcome common causes of clinical inertia in the practice setting.

T2DM Pathophysiology: Current Knowledge
Environmental, genetic, and lifestyle factors contribute to the onset of T2DM, which is characterized by the combination of insulin resistance and relative insulin deficiency, each occurring very early in the disease. Under normal circumstances, islet secretion of insulin facilitates uptake of glucose into tissues such as skeletal muscle and adipose tissue. The interplay between glucose production, uptake, and utilization, along with insulin secretion, maintains normal glucose tolerance.

In those at risk of T2DM, tissue sensitivity to insulin often is reduced and initially is associated with hyperinsulinemia. In the presence of normal or near-normal β-cell function, the compensatory rises in insulin are able to accommodate the enhanced tissue resistance, resulting in hyperinsulinemia. However, patients at risk of T2DM may also exhibit some degree of β-cell dysfunction, which may even be present when glucose tolerance is near-normal. In time, resistance worsens and β-cell function declines in association with impaired fasting glucose and/or impaired glucose tolerance. A decrease in β-cell mass accompanying the dysfunction has been reported in such subjects and is also seen prior to the onset of T2DM. Eventually, insulin secretion is insufficient to compensate for even small increases in insulin demand; postprandial hyperglycemia worsens with increases in fasting plasma glucose that parallel the decline in plasma insulin. This leads to the diagnosis of T2DM.

The insulin secretagogues, such as sulfonylureas and the glinides, can stimulate insulin release from functioning β cells but have no effect on slowing the progression of β-cell dysfunction. Metformin and insulin are also ineffective in this regard.

Contribution of Glucagon
The role of glucagon in the control of glycemia is often under-emphasized or overlooked. Produced by α cells in pancreatic islets, glucagon is secreted in response to low blood levels of glucose, stimulating hepatic generation of glucose via gluconeogenesis or glycogenolysis.
Important differences exist in glucagon responses between subjects with normal glucose tolerance and patients with T2DM. Following a carbohydrate meal in nondiabetic individuals, the response to a rise in blood glucose is the early insulin response, which exerts a paracrine inhibitory effect on \( \alpha \) cells to suppress further glucagon secretion.\(^{32} \) This prevents excessive increases in blood glucose. However, the early insulin response is defective in patients with T2DM, owing to progressive \( \beta \)-cell dysfunction, and it may be totally absent as the disease progresses.\(^{33,34} \) Thus, insulin responses to post-meal elevations are delayed and insufficient to inhibit glucagon secretion. Therefore, glucagon hypersecretion ensues, with unabated hepatic glucose production and large increases in blood glucose. These effects cause or exacerbate postprandial hyperglycemia and contribute to impaired glycemic control.\(^{33,35,36} \)

The inability to prevent or minimize glucagon hypersecretion has represented a major unmet need in T2DM management. Traditional therapy with TZDs, or sulfonylureas, has no major effect on improving early insulin response or the suppression of glucagon.\(^{37} \) The glinides have some effect on early insulin release,\(^{38} \) and metformin has been shown to limit hepatic glucose production,\(^{39} \) but neither controls glucagon. Early studies\(^{32} \) have shown that exogenous insulin administration is also relatively ineffective in attenuating \( \alpha \)-cell glucagon hypersecretion in T2DM.\(^{32} \) Conventional therapies, including insulin, have not adequately controlled postprandial hyperglycemia,\(^{40} \) which is attributed mainly to glucagon hypersecretion. Adequate control of postprandial hyperglycemia is an unmet need in diabetes care.

**Contribution of Incretins**

After development of a radioimmunoassay for insulin in the 1960s, it was realized that the \( \beta \)-cell insulin response in healthy subjects after an oral glucose load was much greater than that after intravenous (IV) glucose when plasma glucose levels were matched (Figure 3).\(^{41} \) The difference in insulin levels between oral and IV glucose became known as the “incretin effect,” because it was shown to be related to meal-stimulated release of incretin hormones from the gastrointestinal tract, which potentiated insulin secretion.

Subsequent research in animals and humans confirmed that incretin effects are essential for maintenance of normal glucose tolerance and that many pathophysiologic abnormalities in T2DM are related, at least in part, to the impaired effect of incretins. The following is a review of endogenous incretin actions and benefits of their exogenous administration that led to the development of the clinically applicable incretin-based therapies.

**Expanding the Understanding of Incretins—Implications for T2DM**

**Physiology of Incretin Hormones**

**Effects of Incretins in Healthy Subjects**

Incretins are gastrointestinal hormones released during nutrient absorption to increase pancreatic insulin secretion in a glucose-dependent manner. The 2 gut peptides accounting for most of the incretin effect are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).\(^{42} \) Both are secreted from specialized gut neuroendocrine cells in response to nutrient ingestion. GIP is secreted by duodenal and proximal jejunal \( \beta \) cells, and GLP-1 is synthesized in L cells found primarily in the distal small bowel and colon.\(^{42,45} \) GLP-1 is found in plasma in 2 biologically active forms, GLP-1(7-37) and GLP-1(7-36) amide; these peptides differ by a single amino acid, and their biologic potencies and plasma half-lives are identical.\(^{42,43} \) “GLP-1” refers to both active peptides.

Within minutes of release from their intestinal sites, GIP and GLP-1 undergo rapid metabolism (proteolytic cleavage) to inactive metabolites by the enzyme dipeptidyl peptidase-IV (DPP-4),\(^{46} \) resulting in very short half-lives of intact hormones (about 5-7 minutes for GIP and 2 minutes for GLP-1).\(^{42,47} \) Most metabolism appears to occur upon entry of the hormone into DPP-4 containing blood vessels that drain the intestinal mucosa.\(^{46} \)

The small amounts of active GLP-1 and GIP that survive this initial cleavage and reach the pancreas act on receptor sites residing on islet \( \beta \) cells to stimulate insulin secretion.\(^{43,45} \) Incretin effects are largely glucose-dependent and differ from those of sulfonylureas, which promote some insulin release from functioning \( \beta \) cells, even in the presence of very low plasma glucose levels.

A second pancreatic effect of GLP-1 is \( \alpha \)-cell inhibition and reduced glucagon hypersecretion, demonstrated by in vitro, animal, and human data.

**Effects of Incretins in T2DM**

Active GLP-1 levels after glucose administration are reduced in T2DM patients.\(^{47,48} \) However, the insulintropic and glucagon-
lowering actions of GLP-1 are partially preserved in T2DM patients, in both fasting and postprandial states.44,49,50

In contrast, plasma levels of GIP are normal or slightly elevated in T2DM, while its incretin activity is markedly defective or absent.45,49,51,52 Thus, both impaired secretion of GLP-1 and defective activity of GIP contribute to the blunted incretin response in T2DM. Some investigators have suggested that each of these impairments may contribute to the initial development of diabetes.49,58,52

The reduced incretin effect observed in T2DM implies a potential therapeutic role of exogenously administered incretin peptides in management of the disease.

Infusion Studies With GIP and GLP-1

The pharmacodynamics of GIP and GLP-1 were investigated in healthy subjects and T2DM patients with the use of continuous IV or subcutaneous (SC) infusions, necessary due to the hormones’ rapid metabolism via DPP-4. The glucose-dependent insulinotropic effects of GIP and GLP-1 infusions were clearly demonstrated by Kreymann and associates in healthy subjects.53

When either GLP-1 or GIP was administered prior to IV glucose load, no effect was seen on basal glucose or insulin, demonstrating the glucose-dependent effect of incretins—β-cell function is stimulated only in the presence of rising or elevated plasma glucose. With IV glucose loading during the test infusions, insulin levels rose in subjects receiving GLP-1 or GIP relative to saline, and glucose levels were lower. Upon discontinuation of IV glucose, there was cessation of incretin action, which limited the occurrence of hypoglycemia. This study also showed that, at matched molar concentrations, GLP-1 has greater secretagogue properties than does GIP in healthy subjects, as evidenced by the larger increase in insulin levels with GLP-1 and lower blood glucose responses.

In a subsequent study by Vilsboll et al.,52 the exogenous insulinotropic effects of these incretin hormones were compared in patients with T2DM. While both peptides produced some early insulin release, which was reduced compared with controls, later-phase insulin levels were much higher with GLP-1 than GIP infusion. Thus, GIP is much less effective in T2DM during prolonged infusion. Therefore, treatment with GLP-1 in T2DM appeared to have potential useful clinical benefit.

As shown in Figure 4, a 4-hour infusion of GLP-1 in hyperglycemic T2DM patients lowered fasting glucose levels, increased insulin, and decreased glucagon until glucose levels reached euglycemia. Insulin then declined and glucagon increased, demonstrating the glucose dependence of the effect of GLP-1 and its diminished potential to produce hypoglycemia.50

Other pharmacodynamic and clinical effects of GLP-1 in T2DM patients seen with continuous IV or SC infusions included increased early and later phases of insulin responses, normalization of fasting and postprandial hyperglycemia, enhancement of insulin sensitivity and β-cell function, improvement in glycemic (A1C) control, decreased gastric emptying, and reduced food intake.32,44,50,54,56

Specific Effects on Satiety and Body Weight

Most T2DM patients are obese,57 and many may find weight loss to be one of the most difficult goals to achieve. This can be related, in part, to the weight gain promoted by some antidiabetic therapies. GLP-1 infusion has been associated with enhanced satiety, reduced food intake, and weight loss or neutrality in studies involving both healthy subjects and T2DM patients.54,56,58,59

It remains unclear whether slowed gastric emptying is the reason for the increased satiety and reduced food intake observed during GLP-1 infusion, as a central mechanism for GLP-1-enhanced satiety has been documented in animal studies.44

Effects on β-Cell Health

Slowing chronic β-cell dysfunction is perhaps the most important goal of research efforts in T2DM. One worrisome aspect of β-cell dysfunction is the loss of β-cell mass, potentially due to increased β-cell apoptosis. In contrast, the capacity for β-cell replication appears to remain relatively normal.34,31

In vitro studies with islet and β-cell primary cultures or cell lines and studies in diabetic rodents have shown β-cell preserving effects of GLP-1 and GIP. An increase in β-cell mass is observed via inhibition of the process of cellular apoptosis and stimulation of β-cell growth (proliferation and neogenesis).13,32,59,60

Farilla et al. demonstrated β-cell preserving actions of GLP-1 in Zucker diabetic rats.61 A 2-day infusion of GLP-1 induced significant increases in insulin secretion, with parallel reductions in glucose levels. Subsequent ex vivo analysis of harvested pancreatic samples from these rats revealed increased islet-cell proliferation and reduced cellular apoptosis. Beta-cell mass and proliferation were increased by 1.6-fold and 1.4-fold, respectively, whereas numbers of apoptotic cells were reduced by 3.6-fold.

Subsequent in vitro studies by this group demonstrated similar benefits in human pancreatic islets; the addition of GLP-1 to freshly isolated islets preserved their morphology and function and reduced cellular apoptosis.60

Incretin-Based Therapies in Clinical Practice

The promising results of infusion and β-cell culture studies with GLP-1 suggest that therapy of T2DM based on incretin hormones might be useful. However, the rapid in vivo degradation by DPP-4 posed a challenge to practical clinical use, as continuous infusion would be required. Two classes of compounds were developed to overcome this obstacle: GLP-1 mimetics and analogues with stability in the presence of DPP-4, resulting in a longer duration of action than GLP-1, and DPP-4 inhibitors that delay endogenous degradation of GLP-1 and GIP, enabling higher plasma levels of the active hormones.54,62

These compounds are collectively known as incretin-based therapies, and 2 have been approved by the U.S. Food and Drug
Administration (FDA)—1 is under FDA review and the other is in late-stage development. These compounds are exenatide, an injectable GLP-1 mimetic (FDA approved); liraglutide, a GLP-1 analogue (phase III); sitagliptin, an oral DPP-4 inhibitor (FDA approved); and vildagliptin, an oral DPP-4 inhibitor currently in FDA review.

GLP-1 Mimetics/Analogues

Exenatide

Exenatide is the synthetic form of exendin-4, a peptide isolated from saliva of the Gila monster. Exendin-4 shares 50% of its amino acid sequence with GLP-1 and has similar affinity for GLP-1 receptor sites. After an SC dose, peak plasma levels of exenatide are seen in about 2 hours. Exenatide is not metabolized in the liver but is eliminated primarily by glomerular filtration, with subsequent proteolytic degradation. The elimination half-life of exenatide is substantially longer than that of GLP-1 (2.4 hours), enabling twice-daily dosing in patients with T2DM.

The initial FDA-approved indication for SC exenatide was adjunctive treatment in T2DM patients not adequately controlled on metformin, sulfonylureas, or both. More recently, the drug has also been approved for use as add-on therapy in T2DM patients not adequately controlled on a TZD. Approved doses are 5 μg and 10 μg twice daily before meals.

Combination With Metformin and Sulfonylureas

In the three 30-week, placebo-controlled studies that were considered collectively for FDA approval of exenatide, doses of 5 μg or 10 μg SC twice daily combined with either a sulfonylurea, metformin, or both were associated with significant dose-related A1C responses. At 30 weeks, an A1C reduction of approximately 0.8% was seen with the 10 μg twice-daily dose in all studies, compared with a slight A1C increase in the placebo groups. Body weight was reduced by 1.6-2.8 kg (mean) in these studies with the 10 μg twice-daily dose and by 0.9-1.6 kg with 5 μg twice daily. Of patients evaluable at

* P<0.05
Adapted from Nauck MA et al. (1993). GLP-1=glucagon-like peptide-1
30 weeks who had a baseline A1C of >7%, 34%-46% and 27%-33% (treated with 10 μg twice daily and 5 μg twice daily, respectively) achieved an A1C of ≤7%. The frequency of hypoglycemia with both doses of exenatide plus metformin was identical to that in the placebo group (each 5%). However, combined with a sulfonylurea, there was a clear and dose-dependent effect, with hypoglycemia occurring in 14% and 36% of patients receiving exenatide 5 μg and 10 μg twice daily, respectively. Dose-related hypoglycemia was also seen with exenatide combined with both a sulfonylurea plus metformin (19% with 5 μg twice daily and 28% with 10 μg twice daily).

An open-label (uncontrolled) extension phase of these studies demonstrated the continued efficacy of SC exenatide for up to 2 years (Figure 5). Lower A1C levels were maintained and body weight decreased, with mean loss of about 4 kg at 2 years.

Comparison With Insulin Glargine
The clinical benefits of insulin glargine (initial dose of 10 units daily titrated upward to achieve a fasting glucose of <100 mg per dL) and exenatide 10 μg twice daily were compared in T2DM patients not well controlled on combination metformin-sulfonylurea therapy. A1C levels were reduced by approximately 1% over 26 weeks after addition of either agent to the prior therapy. Postprandial hyperglycemia was reduced more with exenatide, whereas fasting blood glucose reductions were greater with insulin glargine. Body weight increased significantly during insulin glargine therapy (about 2 kg) but decreased by the same amount in the exenatide group. The overall frequency of hypoglycemia was similar in those receiving exenatide or glargine, with nocturnal hypoglycemic episodes more common with glargine and daytime hypoglycemia more frequent with exenatide. As both agents improved A1C levels comparably, careful consideration of weight differences or side effect profiles by the clinician may be warranted.

Adverse Effects and Tolerability
Hypoglycemia can be therapy-limiting with any antihyperglycemic agent when attempting to achieve tight glucose control and A1C goals. Available data indicate that hypoglycemia is not problematic with exenatide when given with metformin or a TZD but must be considered when given with a sulfonylurea.

The glycemic efficacy of exenatide comes at the expense of relatively frequent gastrointestinal symptoms, which can limit therapy in some patients. Mild-to-moderate nausea occurs in about 40% of patients receiving twice-daily exenatide, with diarrhea and vomiting in less than 15%. However, nausea may subside over time in some patients. Discontinuation rates due to nausea and vomiting were reported to be 3% and 1%, respectively. Patient education is imperative regarding potential gastrointestinal side effects and how to minimize them. Several key points should be communicated: (1) patients should be...
instructed to eat slowly and stop eating when satiated, (2) titration from the 5 µg pen to the 10 µg pen should occur only if the patient is tolerating the 5 µg dose, and (3) injecting within 15 minutes of a meal may lessen early GI distress, but if the patient overeats, late nausea/vomiting could occur when exenatide peaks at ~2 hours after injection. Formation of antibodies to exenatide has been reported in up to 50% of patients treated; these are usually in low titers and have not affected glucose-lowering effects in most. Adverse events attributable to exenatide antibodies have not been documented, and the long-term clinical relevance remains to be determined.

Because exenatide reduces the rate of gastric emptying, it could delay absorption of other drugs. Medications that are affected by delayed oral absorption, such as pain medication and some antibiotics, should be taken 1 hour prior to exenatide dosing. Exenatide is given twice daily, and patient education on techniques for SC injections is essential to enhance adherence.

**Liraglutide**

Liraglutide, a GLP-1 analogue currently in phase III trials, has a longer plasma half-life (10-14 hours) than exenatide after SC doses and can be given once daily. The extended duration of action of liraglutide is related to fatty acid acylation of the compound, which slows absorption and enables binding to interstitial and plasma albumin.

**Comparison With Glimepiride**

In a randomized study, liraglutide 0.6 mg and 0.75 mg SC once daily as monotherapy significantly reduced fasting blood glucose and A1C levels in T2DM patients poorly controlled on an oral antidiabetic agent. Prior therapy in these patients was discontinued before randomization. At these doses of liraglutide, A1C was reduced by 0.70% and 0.75% compared with placebo at 12 weeks, respectively, which was significantly greater than with placebo and comparable with that of glimepiride given in an open-label comparator arm in the study. Lower doses of liraglutide (0.045-0.45 mg per day) were less effective. Body weight decreased slightly with liraglutide, but this did not reach significance at the clinically efficacious doses (0.6 mg and 0.75 mg); in contrast, body weight increased slightly with glimepiride. Hypoglycemia tended to occur more with glimepiride (4 of 26 patients with glimepiride vs. 1 of 135 patients with liraglutide). The proinsulin-to-insulin ratio was significantly reduced by liraglutide but not glimepiride, suggestive of enhanced β-cell efficiency with the GLP-1 analogue.

**Comparison With Glimepiride-Metformin**

The efficacy of liraglutide alone or in combination with metformin was compared with metformin monotherapy or a metformin-glimepiride combination in T2DM patients in double-blind study by Nauck et al. Mean baseline A1C was 9.4%, and after 5 weeks, A1C was reduced by a mean of 1.2% with liraglutide plus metformin, which was statistically superior to either agent alone. The liraglutide-plus-metformin group was the only one to achieve a reduction in A1C >1%. Body weight increased in the metformin-glimepiride group but was reduced by about 2 kg in those receiving liraglutide alone or with metformin. In this study, liraglutide was safely titrated upward from 0.5 mg daily to 2 mg daily in weekly increments of 0.5 mg.

**Adverse Effects and Tolerability**

Hypoglycemia has not been a significant problem with liraglutide (<3% of patients) and occurs less frequently than with glimepiride. Nausea, vomiting, and diarrhea have been the most frequent adverse effects but were generally mild and not therapy-limiting. Antibodies have not been reported in studies to date. Further long-term studies are needed to fully evaluate the adverse event profile of liraglutide.

**DPP-4 Inhibitors**

The approach of preventing the rapid degradation of GLP-1 and GIP in the circulation after meals by inhibiting the enzyme responsible for that degradation has been shown to be clinically useful in T2DM.

The DPP-4 inhibitors discussed here, sitagliptin and vildagliptin, can be given orally and display a long duration of action, with 80% or greater DPP-4 inhibition usually maintained for 24 hours after single doses. They significantly increase plasma levels of intact GLP-1 and GIP, prolong their elimination half-lives, and restore insulinotropic and other effects. Both DPP-4 inhibitors have been shown to significantly stimulate insulin secretion, suppress glucagon secretion, reduce fasting and postprandial glucose levels, potentially improve β-cell function, and decrease A1C values in T2DM patients.

Sitagliptin and vildagliptin are specific and selective for the ubiquitous aminopeptidase enzyme DPP-4. Although other biologically active peptides are also degraded by DPP-4, some with insulin-stimulating properties, animal studies have strongly suggested that GLP-1 is the principal mediator of effects seen with DPP-4 inhibition.

**Sitagliptin**

Sitagliptin, the first FDA-approved DPP-4 inhibitor, is indicated for the treatment of T2DM either as monotherapy or in combination with metformin or a TZD, such as pioglitazone or rosiglitazone, in patients poorly controlled on the single agents. The recommended dose in most patients is 100 mg once daily. Sitagliptin exhibits good oral bioavailability (87%) and can be given without regard to meals; protein binding is low (38%), and hepatic metabolism is minimal, with most of a dose appearing unchanged in the urine. The elimination half-life of sitagliptin is approximately 12 hours.
Monotherapy
In an 18-week, placebo-controlled study involving 521 patients with T2DM, oral doses of sitagliptin, 100 mg or 200 mg once daily, were similarly effective in lowering A1C levels; placebo-subtracted reductions at 18 weeks were 0.6% and 0.48%, respectively. Reductions in A1C were significantly greater in patients with higher baseline A1C values. With doses of 100 mg per day, A1C was reduced by 0.4% and 1.2% in patients with baseline A1C values of < 8% and ≥ 9%, respectively; the 200 mg daily dose was associated with similar changes (0.3% and 1%, respectively). Sitagliptin did not affect body weight, and the incidence of hypoglycemia with sitagliptin (3/205 [1.5%] for 100 mg per day, 2/206 [1.0%] for 200 mg per day) was similar to placebo (0/110).

Comparison With Glipizide
In patients responding inadequately to metformin monotherapy (baseline A1C, 7.5%), similar improvement in glycemic control was seen with addition of sitagliptin 100 mg per day or glipizide (titrated up to 20 mg per day; mean dose of glipizide = 10.3 mg per day) in a large, 1-year randomized trial. At week 52, the mean reduction in A1C was 0.67% in each group. Both sitagliptin and glipizide also reduced fasting plasma glucose (< 10 mg per dL). Hypoglycemic episodes were fewer with sitagliptin (5% vs. 32%), and sitagliptin promoted weight loss (about 1.5 kg) compared with weight gain in the glipizide group.

Combination With Metformin
Combined use of sitagliptin plus metformin was superior to metformin alone in lowering A1C and fasting plasma glucose in T2DM patients in a 6-month placebo-controlled study (Figure 6). A fixed-dose combination of sitagliptin/metformin is approved by the FDA (50/500 mg and 50/1000 mg tablets). When dosing flexibility is necessary, combined use of the individual agents given separately may be preferable in some patients to achieve optimal glucose control.

Combination With Pioglitazone
In a 6-month, randomized trial, sitagliptin added to ongoing pioglitazone therapy was associated with significant reductions in fasting plasma glucose and A1C levels in patients who had not experienced good glycemic control on pioglitazone alone. Significantly more patients receiving sitagliptin plus pioglitazone achieved the target A1C of < 7% than did those treated with pioglitazone-placebo (45% vs. 23%, respectively). There was no additional weight gain from adding sitagliptin to pioglitazone.

Adverse Effects and Tolerability
Sitagliptin has been well-tolerated in clinical studies, with a frequency of hypoglycemia similar to that of placebo. Nasopharyngitis, upper respiratory infection, and headache have occurred in < 3% of patients (placebo subtracted); gastrointestinal disturbances are uncommon. Long-term safety of DPP-4 inhibition will continue to be monitored.

Vildagliptin
Vildagliptin is a highly selective DPP-4 inhibitor that has received an approvable letter from the FDA, though a potential approval date is unknown at this time. Vildagliptin, rapidly and almost
completely (85%) absorbed after oral intake, can be taken without regard to meals. The plasma half-life varies and is approximately 1.5 to 4.5 hours with 25-200 mg dosing. Approximately 55% of the drug is metabolized by hydrolysis, with the majority of the remaining drug eliminated unchanged renally.90

Monotherapy
In a placebo-controlled study, vildagliptin 100 mg orally administered daily for 4 weeks to diet-controlled T2DM patients significantly increased GLP-1 levels and reduced 4-hour post-prandial hyperglycemia, fasting blood glucose, and 24-hour glucose levels.91 Body weight was not significantly affected. Restoration of β-cell and α-cell sensitivity associated with increased levels of GLP-1 was demonstrated in this study. Carefully conducted post-meal (breakfast) studies at 4 weeks showed that levels of insulin were almost identical with vildagliptin and placebo, despite lower plasma glucose levels in the vildagliptin group, which suggested improved β-cell response to glucose with vildagliptin. Glucagon levels were decreased in the vildagliptin group even at the lower glucose levels, reflecting improved sensitivity of α cells to glucose.

Comparison With Metformin
Vildagliptin 50 mg twice daily was compared to metformin 1,000 mg twice daily in a 1-year study involving 780 treatment-naive T2DM patients.76 A1C was reduced by 1% with vildagliptin and by 1.4% with metformin, and this was sustained during the 1-year treatment period. No weight gain was seen with vildagliptin, compared to modest weight loss with metformin. Gastrointestinal adverse effects were significantly more common with metformin.

Comparison With Rosiglitazone
In a 24-week, double-blind comparison, rosiglitazone 8 mg daily and vildagliptin 50 mg twice daily were similarly effective in reducing A1C in drug-naive T2DM patients (Figure 7). Mean A1C levels were reduced by 1.3% and 1.1%, respectively.81 Body weight was not significantly affected by vildagliptin (-0.3 kg) but increased by 1.6 kg in the rosiglitazone group.

Combination Therapy
Combined use of vildagliptin 50 mg daily with metformin 1.5 g to 3 g daily has been shown to prevent deterioration of glycemic control for at least 1 year in T2DM patients in a placebo-controlled study.92 Glycemia improved with the combination (reduction in A1C of 0.6%) but not with placebo plus metformin in the initial 12-week controlled phase (core study). In a subsequent 40-week, blinded extension (1 year total treatment), A1C remained stable with vildagliptin-metformin combination but increased with placebo plus metformin. Body weight decreased slightly and similarly in each group.

Adverse Effects and Tolerability
Vildagliptin has been well tolerated in available trials, though long-term safety will continue to be monitored. Hypoglycemia has been rare. No relationship to dose has been observed for adverse effects, and gastrointestinal tolerability has been superior to metformin.76

Effect of Incretin-Based Therapies on β-Cell Health
Similar to GLP-1, its mimetics and analogues have been shown to promote β-cell preservation by enhancing proliferation and inhibiting apoptotic pathways in islet cell lines and in rodents.43,94,95 Clinically, a significant lowering of the proinsulin-to-insulin ratio has been observed with SC exenatide 5 μg or 10 μg given twice daily in T2DM patients, indicative of improved β-cell function.63 Liraglutide has also improved this ratio.72

With use of mathematical modeling to assess postprandial β-cell function, exenatide 5 μg and 10 μg twice daily was shown to produce increased β-cell dose response and to enhance insulin secretion in T2DM patients.96

DPP-4 inhibitors have also been shown to promote β-cell neogenesis and β-cell preservation, in keeping with data for GLP-1.20,78 A study by Dutteroy et al. showed vildagliptin significantly increased β-cell growth; apoptosis was reduced and β-cell mass increased.97

An increased β-cell response to glucose, in association with increased GLP-1 plasma levels, was demonstrated clinically by Mari and colleagues99 in T2DM patients receiving oral vildagliptin; they employed a modeling approach similar to that for
exenatide to assess β-cell function. Clinical studies have shown an improvement in the proinsulin-to-insulin ratio during therapy with sitagliptin or vildagliptin.83,87,88,100

In summary, either a GLP-1 mimetic/anogue or DPP-4 inhibitor can improve glycemic control in T2DM by producing clinical effects first noted with a continuous infusion of GLP-1. The oral route and weight neutrality are advantages of DPP-4 inhibitors, whereas potential weight loss is an advantage of the GLP-1 mimetics/analogues. Both classes of agents have been shown to preserve β-cell function in vitro. A summary of key aspects of each class is included in the Table.

### Conclusion

The prevalence of T2DM remains on the rise in the United States. Two thirds of those diagnosed have not achieved adequate blood glucose control and are at a high risk of developing complications. Clinical inertia is an important contributing factor to treatment failure. It is also the factor that can be improved through more specific diagnosis, more complete patient education, and an emphasis on earlier and more aggressive therapy of T2DM in goal-oriented fashion. Based largely on the underlying pathophysiology of T2DM, newer ACE/AACE guidelines have been developed to facilitate this more aggressive approach. The incretin-based therapies can favorably impact some underlying elements in T2DM pathophysiology, including glucagon hypersecretion, rapid gastric emptying, postprandial hyperglycemia, and possibly chronic β-cell dysfunction. When incorporated early into a long-term, treat-to-target management plan, incretin-based therapies have the potential of reducing the prevalence of treatment failure in T2DM and may have an impact on disease progression.

### DISCLOSURES

This article is based on a presentation given by the authors at a symposium held April 11, 2007, at the Academy of Managed Care Pharmacy’s 19th Annual Meeting and Showcase in San Diego, California. Author Curtis Triplitt has been a consultant to, has received honoraria for presentations from, has been an investigator or subinvestigator in clinical trials sponsored by, and/or has received research support from the following companies: Amylin Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche & Co., and Pfizer Inc. Author Janet B. McGill has been a consultant to, has received honoraria for presentations from, has been an investigator or subinvestigator in clinical trials sponsored by, and/or has received research support from the following companies: Amylin Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Daichi Sankyo, Inc., DaiMedica Inc., FivePrime Therapeutics, Inc., GlaxoSmithKline, Johnson & Johnson; Kowa Research Institute, Inc.; MannKind Corporation; Merck & Co., Inc.; Meta Cure; Novartis Pharmaceuticals Corporation; and Sanofi-Aventis. Author Christopher S. Conner discloses no potential bias or conflict of interest relating to this research.

### TABLE

<table>
<thead>
<tr>
<th>Action</th>
<th>Injectable GLP-1 Mimetic/Anologue</th>
<th>Oral DPP-4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin secretion</td>
<td>Enhanced</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>Suppressed</td>
<td>Suppressed</td>
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<tr>
<td>Postprandial hyperglycemia</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Slowed significantly</td>
<td>Marginal or no significant effect</td>
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<tr>
<td>Appetite</td>
<td>Suppressed</td>
<td>No obvious effect</td>
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<tr>
<td>Satiety</td>
<td>Induced</td>
<td>No obvious effect</td>
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<tr>
<td>Body weight</td>
<td>Reduced</td>
<td>Neutral</td>
</tr>
<tr>
<td>β-cell function</td>
<td>Preservation (in vitro/animal data); pro-insulin/insulin ratio improved clinically</td>
<td>Preservation (in vitro/animal data); pro-insulin/insulin ratio improved clinically</td>
</tr>
<tr>
<td>Gastrointestinal adverse effects</td>
<td>Often</td>
<td>Rare to none</td>
</tr>
<tr>
<td>Clinical antibody formation</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Adapted from references.42,44,54,56,84,78
† Based on available data.

GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-IV

### REFERENCES


The Changing Landscape of Type 2 Diabetes: The Role of Incretin-Based Therapies in Managed Care Outcomes


The Changing Landscape of Type 2 Diabetes: The Role of Incretin-Based Therapies in Managed Care Outcomes


Clinical inertia in T2DM can be minimized by:
- early diagnosis.
- earlier aggressive therapy.
- adopting newer goal-oriented guidelines.
- greater patient education.
- all of the above.

In addition to clinical inertia, which of the following contributes to the failure to achieve and maintain glycemic goals in T2DM?
- Progressive β-cell dysfunction.
- Weight loss induced by traditional therapies.
- Failure of traditional therapies to increase glucagon secretion.
- Overuse of insulin.
- (a) and (c) are correct.

The incretin effect can be defined as:
- the process by which the pancreas produces insulin.
- the amount of insulin produced as a result of incretin release.
- the difference in blood glucose levels after different glucose loads.
- the difference in insulin response to oral and intravenous glucose loads.
- none of the above.

Continuous infusion of GLP-1 has been shown to promote which of the following effects in T2DM patients:
- Restoration of the first- and second-phase insulin response.
- Decreased secretion of glucagon.
- Normalization of fasting and postprandial hyperglycemia.
- A decrease in A1C levels.
- All of the above.

In the 30-week, placebo-controlled studies considered for FDA approval of exenatide, a reduction in A1C of about 0.8% was seen with the 10 μg twice-daily dose and body weight was significantly reduced.
- True.
- False.

Which of the following about the occurrence of hypoglycemia during exenatide therapy is true?
- It is not problematic when given with a sulfonylurea.
- It is common when combined with metformin.
- Nocturnal hypoglycemia has been more common with exenatide than with insulin glargine.
- Hypoglycemic episodes have been seen in slightly more than one third of patients treated with exenatide 10 μg twice daily plus a sulfonylurea.
- The frequency of hypoglycemia during the daytime is similar with exenatide and insulin glargine.

Which of the following about sitagliptin is false?
- It exhibits good oral bioavailability.
- It has an elimination half-life of about 12 hours.
- It produces an approximate 2-fold rise in GLP-1.
- Hepatic metabolism is extensive.
- Endogenous DPP-4 enzyme is inhibited by 80%.

Sitagliptin was non-inferior for improving glycemic control compared with glipizide when these agents were added to metformin therapy in a randomized study, but weight loss was greater in the glipizide group.
- True.
- False.

Vildagliptin has a different mechanism of action than sitagliptin.
- monotherapy has produced similar reductions in A1C as rosiglitazone monotherapy and metformin monotherapy in separate clinical studies involving previously untreated patients.
- has not been shown to improve β-cell responses to glucose.
- produces hypoglycemia much more frequently than sitagliptin.
- produces a higher frequency of gastrointestinal adverse effects than metformin.

Promotion of β-cell neogenesis and preservation has been observed in animal and in vitro studies with both GLP-1 mimetics/analogues and DPP-4 inhibitors.
- True.
- False.