Efficacy and Safety of Incretin-Based Therapies in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

This article aims to provide an overview of efficacy and safety data on glucagon-like peptide–1 (GLP-1) receptor agonists and dipeptidyl peptidase–4 (DPP-4) inhibitors in the treatment of type 2 diabetes mellitus. Our goal is to differentiate the clinical profiles of GLP-1 receptor agonists and DPP-4 inhibitors, as well as the individual agents within each class. Additionally, we examine the utility of GLP-1 receptor agonists and DPP-4 inhibitors as these agents may be applied at different stages of type 2 diabetes therapy and discuss recently published clinical findings and their implications for treatment.

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KEYWORDS: DPP-4; exenatide-LAR; GLP-1 receptor agonist; liraglutide; sitagliptin

The current pandemic of diabetes mellitus and projections for future growth in the prevalence of the disease threaten to create a global health crisis. Findings from clinical trials provide clear and compelling evidence that intensive treatment of type 2 diabetes can significantly reduce the risk of disease-associated cardiovascular and renal complications. Safe and effective treatments for diabetes may mitigate, though certainly not dispel, the looming public health crisis. Although many therapies for type 2 diabetes exist, including insulin secretagogues and insulin sensitizers, success in diabetes is fleeting. Treatment is characterized by progressive diminution of effect, leading almost inevitably to treatment failure. As monotherapies fail, additional agents are added. Glycemic control is stabilized, but sometimes at the cost of side effects such as weight gain or hypoglycemia, which themselves may undermine therapeutic effect. Eventually even combinations of oral agents fail, necessitating the introduction of insulin. Clearly there is a continuing need to add to the armamentarium of safe and effective antidiabetic remedies, with better risk-benefit ratios and greater patient acceptability.

Impairment of incretin activity plays an integral part in the metabolic derangement underlying type 2 diabetes. Glucagon-like peptide–1 (GLP-1) receptor agonists and dipeptidyl peptidase–4 (DPP-4) inhibitors represent the 2 classes of incretin therapies currently available. GLP-1 receptor agonists enhance incretin activity by providing pharmacologic levels of human GLP-1 receptor stimulation, whereas DPP-4 inhibitors exert their effects by slowing the degradation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Incretin-based therapies enhance endogenous insulin secretion without causing hypoglycemia or weight gain. This review focuses on the efficacy and safety of incretin therapies, and the utility of their application at different stages in the progression of diabetes. It must also be recognized that diabetes is quite commonly accompanied by multiple comorbid conditions; diabetes agents that would benefit, or at least not worsen, common comorbidities (e.g., obesity, hypertension, dyslipidemia) are highly desirable.

Exenatide is a synthetic, 39- amino acid peptide form of the exendin-4 molecule first isolated from the salivary gland secretions of the Gila monster. It shares 53% homology with mammalian GLP-1 but is resistant to enzymatic degradation by DPP-4. It was the first approved therapeutic agent in the incretin class of medications, and acts by mimicking the physiologic actions of native GLP-1. Exenatide is administered twice daily within 60 minutes of morning and evening meals. Differences in the N-terminal amino acid sequence of exenatide from that of native GLP-1 confer resistance to the effects of DPP-4, substantially in-
creasing its half-life in the circulation (approximately 2.4 hours compared with 1 to 2 minutes for native GLP-1). The duration of effect of exenatide is therefore substantially longer than that of native GLP-1, although twice-daily administration is required. Exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation; hence it is contraindicated in patients with end-stage renal disease or severe renal impairment. Exenatide is not recommended in patients with severe gastrointestinal disease. In a small proportion of patients, formation of antibodies at high titers could result in the failure of exenatide to achieve adequate improvement in glycemic control. Exenatide is available in the United States; it is indicated for adjunctive therapy to improve glycemic control in patients with type 2 diabetes that is inadequately controlled on metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

Liraglutide is a once-daily human GLP-1 analog with 97% homology with human GLP. Modifications to the molecule include 1 amino acid substitution and the attachment of a fatty acid chain with a glutamoyl spacer to a lysine residue. Those adjustments slow the absorption and retard the degradation of liraglutide by the proteolytic enzyme DPP-4, prolonging the half-life to 13 hours. The route of elimination of liraglutide appears to be by generalized proteolysis, with no single organ system having demonstrated major involvement; hence no dosage adjustment appears to be necessary in patients with severe renal impairment or hepatic insufficiency. Liraglutide is currently under review by the US Food and Drug Administration (FDA).

DPP-4 inhibitors are oral agents that prolong the bioactivity of native GLP-1 (and GIP) by inhibiting the proteolytic activity of the DPP-4 enzyme. DPP-4 inhibitors have been shown to elevate active GLP-1 levels 2- to 3-fold by decreasing its half-life in the circulation (approximately 2.4 hours compared with 1 to 2 minutes for native GLP-1). The duration of effect of exenatide is therefore substantially longer than that of native GLP-1, although twice-daily administration is required. Exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation; hence it is contraindicated in patients with end-stage renal disease or severe renal impairment. Exenatide is not recommended in patients with severe gastrointestinal disease. In a small proportion of patients, formation of antibodies at high titers could result in the failure of exenatide to achieve adequate improvement in glycemic control. Exenatide is available in the United States; it is indicated for adjunctive therapy to improve glycemic control in patients with type 2 diabetes that is inadequately controlled on metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

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DPP-4 inhibitors are oral agents that prolong the bioactivity of native GLP-1 (and GIP) by inhibiting the proteolytic activity of the DPP-4 enzyme. DPP-4 inhibitors have been shown to elevate active GLP-1 levels 2- to 3-fold by providing up to 90% inhibition of plasma DPP-4 activity over 24 hours in vivo. Sitagliptin is the only DPP-4 inhibitor currently available in the United States. A combination tablet containing sitagliptin and metformin is also available. Approximately 79% of the sitagliptin dose is excreted unchanged in the urine; metabolism is a minor pathway of elimination. Dosage adjustment is recommended in patients with moderate or severe renal impairment, and in patients with end-stage renal disease requiring dialysis. Post-marketing reports of serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens-Johnson syndrome have been noted in patients on sitagliptin. Vildagliptin, another DPP-4 inhibitor, has been approved for use in the European Union and other countries. Vildagliptin is primarily metabolized by liver hydrolysis and is contraindicated in patients with severe hepatic dysfunction. Vildagliptin has been associated with changes in liver enzyme levels and, in animal models, with skin lesions including blistering and ulceration. Approval in the United States is pending additional trials in patients with renal dysfunction.

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EFFICACY OF INCRETIN-BASED THERAPIES IN PATIENTS FAILING DIET OR EXERCISE

A randomized, double-blind, 24-week monotherapy trial compared twice-daily exenatide 5 µg, exenatide 10 µg, and placebo in 232 patients with type 2 diabetes inadequately controlled by diet and exercise alone. Compared with placebo, exenatide 5 µg and 10 µg demonstrated significantly greater mean reductions in hemoglobin A₁c (HbA₁c) (P = 0.003 and P < 0.001 for the 5-µg and 10-µg doses, respectively), fasting plasma glucose (FPG) (P = 0.029 and P = 0.016), and body weight (Table 1 and Figure 1). The proportion of patients achieving HbA₁c ≤7% at study endpoint was 48% in the 5-µg group (P = 0.024) and 46% in the 10-µg group (P = 0.036) versus 29% in the placebo group. The incidence of nausea was significantly greater in the combined exenatide groups (8%) relative to placebo (0%; P = 0.010), whereas hypoglycemia rates were slightly, although not significantly, higher in patients receiving exenatide 5 µg (5%) or exenatide 10 µg (4%) relative to placebo (1%).

A long-acting–release (LAR) formulation of exenatide (once weekly administration) is currently in phase 3 clinical development. In a phase 2 study, exenatide-LAR (0.8 or 2.0 mg) was administered for 15 weeks to patients with type 2 diabetes whose disease was suboptimally controlled with metformin and or/diet and exercise (N = 45). Mean HbA₁c levels were reduced significantly with both exenatide-LAR doses compared with placebo (P < 0.0001) (Figure 1). Only the 2.0-mg dose was associated with a significant mean body weight reduction versus placebo (P < 0.05) (Table 1). Hypoglycemia was reported in 25% of patients in the 0.8-mg dose group (n = 16) and in no patients in the 2.0-mg dose group (n = 15). Nausea was reported in 19% and 27% of the patients who received exenatide-LAR at the 0.8 and 2.0 mg doses, respectively, and in 15% of patients who received placebo. Injection-site bruising was observed in 13% and 7% of patients in the 0.8 and 2.0 mg groups, respectively. Exenatide LAR injections were administered by study site staff.

In a 14-week phase 2 monotherapy trial, HbA₁c reductions observed with liraglutide 1.9 mg and 1.25 mg once daily were –1.45% and –1.40% versus placebo (1%). The percentage of patients reaching the target HbA₁c goal of ≤7% was 46% with liraglutide 1.9 mg and 48% with liraglutide 1.25 mg versus 5% for placebo. Patients on the highest dose of liraglutide realized significant reductions in systolic blood pressure compared with patients given placebo, –7.9 mm Hg (P = 0.0023). Garber and colleagues randomized 746 patients with type 2 diabetes to 52 weeks of double-blind monotherapy with liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, or glimepiride 8 mg/day. Patients had previously experienced inadequate glycemic control while treated with diet and exercise alone or up to a half-maximal dose of a single oral agent. Each liraglutide dose reduced mean HbA₁c to a significantly greater extent than glimepiride (P = 0.0014 for 1.2 mg and
which has been seen with the GLP-1 receptor agonists.

have demonstrated weight neutrality rather than weight loss, these studies, DPP-4 inhibitors have been well tolerated and therapy have been evaluated in a number of clinical trials. In 

HbA1c with liraglutide 1.8 mg; that reduction was main-

drug-naive population) experienced a –1.6% decrease in liraglutide versus glimepiride (Table 1). The subgroup pre-

body weight were significantly greater with either dose of 

P <0.0001 for 1.8 mg) (Figure 1). Reductions in FPG and body weight were significantly greater with either dose of 

Table 1 Fasting Glucose and Weight Reduction of Incretin Therapies as Monotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Baseline Fasting Serum Glucose (mg/dL)*</th>
<th>Δ Fasting Serum Glucose (mg/dL)*</th>
<th>Baseline Weight (kg)</th>
<th>Δ Weight (kg)</th>
</tr>
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<tbody>
<tr>
<td>Exenatide18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 μg bid</td>
<td>166</td>
<td>–17.5 (P = 0.029)†</td>
<td>85</td>
<td>–2.8 (P = 0.004)†</td>
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<tr>
<td>10 μg bid</td>
<td>154</td>
<td>–18.7 (P = 0.016)†</td>
<td>86</td>
<td>–3.1 (P = 0.001)†</td>
</tr>
<tr>
<td>Placebo</td>
<td>160</td>
<td>–5.2</td>
<td>86</td>
<td>–1.4</td>
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<tr>
<td>Exenatide-LAR6</td>
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</tr>
<tr>
<td>0.8 mg once weekly</td>
<td>186</td>
<td>–43 (P &lt;0.001)†</td>
<td>107</td>
<td>Negligible</td>
</tr>
<tr>
<td>2.0 mg once weekly</td>
<td>168</td>
<td>–40 (P &lt;0.001)‡</td>
<td>110</td>
<td>–3.8 (P &lt;0.05)†</td>
</tr>
<tr>
<td>Placebo</td>
<td>184</td>
<td>+18</td>
<td>101</td>
<td>Negligible</td>
</tr>
<tr>
<td>Liraglutide19,20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 mg qd</td>
<td>168</td>
<td>–15 (P = 0.027)‡</td>
<td>92.5</td>
<td>–2.05 (P &lt;0.0001)†</td>
</tr>
<tr>
<td>1.8 mg qd</td>
<td>171</td>
<td>–26 (P = 0.027)‡</td>
<td>92.8</td>
<td>–2.45 (P &lt;0.0001)†</td>
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<tr>
<td>Sitagliptin21</td>
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</tr>
<tr>
<td>100 mg qd</td>
<td>171</td>
<td>–13 (P ≤0.001)§</td>
<td>85.0</td>
<td>–0.2 (P &lt;.01)§</td>
</tr>
<tr>
<td>200 mg qd</td>
<td>175</td>
<td>–16 (P ≤0.001)§</td>
<td>83.7</td>
<td>–0.1 (P &lt;.01)§</td>
</tr>
<tr>
<td>Placebo</td>
<td>177</td>
<td>+5</td>
<td>85.0</td>
<td>–1.1</td>
</tr>
<tr>
<td>Sitagliptin22</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg qd</td>
<td>180</td>
<td>–13 (P &lt;0.001)‡</td>
<td>—</td>
<td>–0.6</td>
</tr>
<tr>
<td>200 mg qd</td>
<td>184</td>
<td>–11 (P &lt;0.01)‡</td>
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<td>–0.2</td>
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<tr>
<td>Placebo</td>
<td>184</td>
<td>+7</td>
<td>—</td>
<td>–0.7</td>
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<td>Vildagliptin23</td>
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<tr>
<td>100 mg qd</td>
<td>189</td>
<td>–16 (P &lt;0.001)‡</td>
<td>91.4</td>
<td>+0.3 (P &lt;0.17)†</td>
</tr>
</tbody>
</table>

LAR = long-acting release.
*1 mg/dL = 0.5551 mmol/L.
†Significance vs. baseline.
‡Significance vs. comparator.
§Significance vs. placebo.
§Significance with least-squares mean difference vs. placebo.
Adapted from Diabetes Care,5,21 Clin Ther,18 Lancet,18 European Association for the Study of Diabetes,20 Diabetologia,22 and Diabet Med.23

P <0.001 for 1.8 mg) (Figure 1). Reductions in FPG and body weight were significantly greater with either dose of liraglutide versus glimepiride (Table 1). The subgroup previously treated with diet and exercise alone (thus a true drug-naive population) experienced a –1.6% decrease in HbA1c with liraglutide 1.8 mg; that reduction was maintained for the full 52 weeks of the study. In the overall study population, a significantly greater proportion of patients treated with liraglutide 1.2 mg (43%) and 1.8 mg (51%) reached target HbA1c ≤7% compared with those treated with glimepiride (28%; P <0.001 for both liraglutide doses versus glimepiride). Nausea was the most frequently experienced adverse event with liraglutide (27.5% incidence for 1.2 mg and 29.3% for 1.8 mg versus 8.5% for glimepiride), but was generally transient. Minor hypoglycemia occurred in 12% of patients treated with liraglutide 1.2 mg, 8% of those treated with liraglutide 1.8 mg, and 24% of those treated with glimepiride. There was no incidence of major hypoglycemia.19

The efficacy and safety of DPP-4 inhibitors as monotherapy have been evaluated in a number of clinical trials. In these studies, DPP-4 inhibitors have been well tolerated and have demonstrated weight neutrality rather than weight loss, which has been seen with the GLP-1 receptor agonists.

Aschner and associates21 conducted a 24-week study of sitagliptin 100 mg or 200 mg monotherapy versus placebo (N = 741) in patients with type 2 diabetes not on an oral antidiabetes agent. HbA1c and FPG were reduced significantly versus placebo by both sitagliptin doses (P <0.001 for both endpoints) (Figure 1 and Table 1). Sitagliptin also increased the proportion of patients who achieved a goal HbA1c ≤7% (41% for 100 mg and 45% for 200 mg versus 17% with placebo, P <0.001). Similarly low rates of hypoglycemia were observed in all treatment groups. There was no change in body weight from baseline with sitagliptin.21 Comparable glycemic results were reported in an 18-week trial of sitagliptin 100 mg or 200 mg monotherapy versus placebo (N = 521). Patients were either drug-naive or had discontinued oral antidiabetic drugs before a run-in period of treatment with diet and exercise alone. The safety data showed a similarly low incidence of hypoglycemia across both sitagliptin groups and the placebo group. There was no significant reduction in body weight in either sitagliptin treatment group (Figure 1 and Table 1).22

In a 52-week study comparing vildagliptin 50 mg twice daily and metformin 1,000 mg twice daily in drug-naive patients, Schweizer and coworkers23 reported that both drugs significantly reduced HbA1c and FPG from baseline.
(P < 0.001 for both endpoints) (Figure 1 and Table 1).
However, statistical noninferiority of vildagliptin 50 mg
twice daily to metformin 1,000 mg twice daily was not
established. A total of 35% of patients treated with vilda-
gliptin and 45% of patients treated with metformin reached
good HbA1c 7%. Patients receiving vildagliptin experi-
enced a modest weight gain; there was a modest reduction
in body weight among patients given metformin (–1.9 kg)
(Table 1). The proportion of patients who experienced
at least one gastrointestinal adverse event was twice as high with
metformin (44%) compared with vildagliptin (22%).

EFFICACY OF INCREDIN-BASED THERAPIES
WHEN COMBINED WITH METFORMIN

Randomized, double-blind, phase 3 clinical trials have dem-
strated the efficacy and safety of GLP-1 receptor agonists
in patients who fail to meet treatment goals when treated
with metformin alone. In a 30-week trial, treatment with
exenatide 10 µg twice daily, dosed 15 minutes before break-
fast and dinner, resulted in significant reductions in HbA1c
(P <0.001), FPG (P <0.05 in the exenatide cohort titrated
to 10 µg twice daily), and weight (P <0.001 in patients in
the 10-µg twice-daily group with baseline body mass index
≥30) compared with placebo (Figure 2 and Table 2).12,25-28
A total of 46% of patients treated with the combination of
exenatide and metformin achieved HbA1c 7%, compared
with 11% of patients receiving metformin monotherapy.
Nausea was reported in 45% of patients treated with met-
formin and exenatide cotherapy; 12% of patients experi-
enced vomiting while using the combination treatment. The
incidence of mild-to-moderate hypoglycemia was 5% in
both the exenatide plus metformin group and the metformin
monotherapy group.25

A 26-week trial (N = 1,091) compared liraglutide (0.6,
1.2, or 1.8 mg/day), glimepiride (4 mg/day), or placebo all
in combination with metformin in patients previously
treated with oral antidiabetic monotherapy or combination
therapy. HbA1c reductions achieved with liraglutide at all
doses were significantly superior to placebo (P <0.0001),
and reductions with liraglutide 1.2 and 1.8 mg were nonin-
fierior to glimepiride (Figure 2). Improvements in HbA1c
with liraglutide were greatest in the subgroup of patients

![Figure 1](image-url) Glycemic effect of incretin therapeutics as monotherapy. HbA1c = hemoglobin A1c; LAR = long-acting release. *Not
currently approved for use in the United States; †not currently approved for use in the United States or European Union; ‡significant vs.
baseline; †significant vs. comparator drug; ‡significant vs. placebo; §not currently approved as monotherapy. (Adapted from Diabetes Care,21
Clin Ther,18 Lancet,19 European Association for the Study of Diabetes,20 Diabetologia,22 and Diabet Med.23)
previously treated with oral agent monotherapy (e.g., -1.30% for the liraglutide 1.8 mg monotherapy group versus 0.71% for the liraglutide 1.8 mg combination group). The proportion of patients in the overall study population who achieved HbA1c ≤7% was 28% and 42% for liraglutide 0.6 and 1.8 mg, respectively, 11% for placebo, and 36% for glimepiride; all liraglutide doses were significantly superior to placebo. Reductions in FPG at all liraglutide doses were significantly superior to placebo (P < 0.0001) and comparable to glimepiride; reduction in body weight was significantly greater with each dose of liraglutide compared with glimepiride (P < 0.0001), and the 1.2-mg and 1.8-mg doses were significantly better compared with placebo (P ≤ 0.01) (Table 2). Gastrointestinal complaints were the most frequent adverse effects, with nausea occurring in 11% to 19% of patients treated with liraglutide, although nausea incidence declined to <4% of patients per week after 16 weeks. No patient experienced major hypoglycemia, and the incidence of minor hypoglycemic events was 0.8% and 3.3% for liraglutide 0.6 and 1.8 mg, respectively, 2.5% for placebo, and 16.9% for glimepiride.  

In a 24-week study, Charbonnel and colleagues evaluated the addition of sitagliptin 100 mg daily or placebo to the treatment of 701 patients with type 2 diabetes failing metformin (>1,500 mg/day) monotherapy. Sitagliptin significantly reduced mean HbA1c and FPG levels compared with placebo (Figure 2 and Table 2). A larger percentage of patients treated with sitagliptin reached HbA1c goal of ≤7% compared with patients given placebo (47% versus 18%; P < 0.001). The addition of sitagliptin or placebo to metformin therapy resulted in a similarly low incidence of hypoglycemia. Small decreases from baseline in body weight were observed in both treatment arms; between-group differences were not significant (Table 2). Initial combination therapy with sitagliptin and metformin provided significant (P < 0.001) reductions in HbA1c over either agent alone in a 24-week study. The addition of vildagliptin to the regimens of patients failing metformin monotherapy produced similar results in a study of similar length (Figure 2). In neither trial were rates or severity of adverse events significantly increased by the addition of a gliptin.

### Efficacy of Incretin-Based Therapies When Combined with a Sulfonylurea

Buse and colleagues conducted a randomized, placebo-controlled, 30-week trial of twice-daily exenatide 5 μg or 10 μg added to the treatment of patients failing sulfonylurea monotherapy versus sulfonylurea therapy alone. Mean HbA1c was reduced significantly in both exenatide groups compared with the group continued on sulfonylurea plus placebo (P < 0.001) (Figure 3). The reduction in FPG was significant only in...
The exenatide 10 μg twice-daily group (Table 3) signiﬁcantly larger percentage of patients reached HbA1c goal of ≤7% in the exenatide groups than in the sulfonylurea plus placebo group (27% to 34% vs. 8%). Patients in the exenatide 10-μg bid, but not the 5-μg bid group, experienced significantly greater weight loss from baseline compared with patients in the sulfonylurea plus placebo group (P < 0.05) (Table 3). Common adverse events with exenatide 5 to 10 μg bid included nausea (39% to 51%), vomiting (10% to 13%), and mild-to-moderate hypoglycemia (14% to 36%).

### Table 2
**Fasting Glucose and Weight Reduction of Incretin Therapeutics in Combination with Metformin**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Baseline Fasting Serum Glucose (mg/dL)*</th>
<th>Δ Fasting Serum Glucose (mg/dL)*</th>
<th>Baseline Weight (kg)</th>
<th>Δ Weight (kg)</th>
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<tbody>
<tr>
<td>Exenatide&lt;sup&gt;25&lt;/sup&gt;</td>
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<tr>
<td>5 μg bid</td>
<td>176</td>
<td>−7 (P &lt; 0.005)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>100</td>
<td>−1.6 (P &lt; 0.001)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>10 μg bid</td>
<td>168</td>
<td>−10 (P = 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>101</td>
<td>−2.8 (P &lt; 0.001)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo</td>
<td>170</td>
<td>+14</td>
<td>100</td>
<td>−0.3</td>
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<tr>
<td>Liraglutide&lt;sup&gt;26&lt;/sup&gt;</td>
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<tr>
<td>0.6 mg qd</td>
<td>184</td>
<td>−20 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>—</td>
<td>−1.8 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
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<tr>
<td>1.2 mg qd</td>
<td>178</td>
<td>−29 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>—</td>
<td>−2.6 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>1.8 mg qd</td>
<td>182</td>
<td>−31 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
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<td>−2.8 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
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<tr>
<td>Placebo</td>
<td>180</td>
<td>+7</td>
<td>—</td>
<td>−1.5</td>
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<tr>
<td>Sitagliptin&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>100 mg qd (+Met ≥1,500 mg qd)</td>
<td>169</td>
<td>−16 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>—</td>
<td>−0.6 to −0.7 (P &lt; 0.05)&lt;sup&gt;§&lt;/sup&gt;</td>
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<tr>
<td>Placebo</td>
<td>173</td>
<td>+9</td>
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<td>−0.6 to −0.7</td>
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<tr>
<td>50 mg qd</td>
<td>175</td>
<td>−2 (P = 0.0003)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>92.5</td>
<td>−0.4</td>
</tr>
<tr>
<td>100 mg qd</td>
<td>178</td>
<td>−18 (P &lt; 0.001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>95.3</td>
<td>+0.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>182</td>
<td>+13</td>
<td>94.8</td>
<td>−1.0</td>
</tr>
</tbody>
</table>

*1 mg/dL = 0.5551 mmol/L.
†Significance vs. placebo.
‡Significance vs. comparator.
§Significance vs. baseline.
Adapted from *Diabetes Care*.<sup>12,25-28</sup>

### Table 3
**Fasting Glucose and Weight Reduction of Incretin Therapeutics in Combination with Sulfonylurea**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Baseline Fasting Serum Glucose (mg/dL)*</th>
<th>Δ Fasting Serum Glucose (mg/dL)*</th>
<th>Baseline Weight (kg)</th>
<th>Δ Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 μg bid</td>
<td>180</td>
<td>−5</td>
<td>95.0</td>
<td>−0.9</td>
</tr>
<tr>
<td>10 μg bid</td>
<td>178</td>
<td>−11 (P &lt; 0.05)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>95.0</td>
<td>−1.6 (P &lt; 0.05)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo</td>
<td>195</td>
<td>+7</td>
<td>99.0</td>
<td>−0.6</td>
</tr>
<tr>
<td>Liraglutide&lt;sup&gt;29&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 mg qd</td>
<td>180</td>
<td>−13 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>82.6</td>
<td>+0.7</td>
</tr>
<tr>
<td>1.2 mg qd</td>
<td>177</td>
<td>−29 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>80.0</td>
<td>+0.3</td>
</tr>
<tr>
<td>1.8 mg qd</td>
<td>175</td>
<td>−31 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>83.0</td>
<td>−0.2 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo</td>
<td>171</td>
<td>+18</td>
<td>81.9</td>
<td>−0.1</td>
</tr>
<tr>
<td>Sitagliptin&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg qd</td>
<td>181</td>
<td>−4.4 (P &lt; 0.001)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>86.5</td>
<td>+0.8 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo</td>
<td>182</td>
<td>+15.7</td>
<td>85.9</td>
<td>−0.4</td>
</tr>
<tr>
<td>Vildagliptin&lt;sup&gt;32&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg qd</td>
<td>189</td>
<td>−5</td>
<td>91.5</td>
<td>−0.1 (P = 0.409)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>50 mg bid</td>
<td>189</td>
<td>−7</td>
<td>87.3</td>
<td>+1.3 (P &lt; 0.0001)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo</td>
<td>186</td>
<td>+4</td>
<td>89.4</td>
<td>−0.4</td>
</tr>
</tbody>
</table>

*1 mg/dL = 0.5551 mmol/L.
†P values represent significance vs. placebo.
‡P values represent significance vs. comparator.
Adapted from *Diabet Med.*,<sup>29</sup> *Diabetes Care.*,<sup>30</sup> and *Diabetes Obes Metab.*<sup>31,32</sup>
A 26-week, double-blind study compared the combination of liraglutide (0.6 mg/day, 1.2 mg/day, and 1.8 mg/day), rosiglitazone (4 mg/day), or placebo with glimepiride therapy in 1,041 patients with type 2 diabetes (Table 3). All liraglutide doses achieved HbA1c reductions that were significantly superior to placebo (P<0.0001) (Figure 3); reductions observed with liraglutide 1.2 and 1.8 mg were significantly superior to rosiglitazone (P<0.0001). The proportion (42%) of patients in the liraglutide 1.8-mg group who achieved HbA1c ≤7% significantly (P=0.0003) exceeded the proportions of rosiglitazone (22%) and placebo (8%) patients who achieved this goal. FPG reductions with all doses of liraglutide were significantly superior to placebo (P<0.0001) (Figure 3), and liraglutide 1.2 and 1.8 mg doses were significantly superior to rosiglitazone (P<0.006). Weight changes in the liraglutide groups were modest, possibly reflecting background sulfonylurea therapy or the relatively low baseline weight of the subjects. Adverse effects associated with liraglutide tended to be gastrointestinal; ≤11% of patients in the liraglutide groups experienced nausea, with the highest incidence reported in the initial 4 weeks of treatment. One major hypoglycemic episode occurred in the liraglutide 1.8-mg group, but it was considered likely to be related to glimepiride. Minor hypoglycemia occurred at a rate of ≤0.5 events per patient-year with all treatments.

Hermansen and coworkers assessed the efficacy and safety of sitagliptin in a 24-week placebo-controlled trial of patients with type 2 diabetes inadequately controlled on glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin 100 mg daily to the patients’ current regimen significantly reduced baseline HbA1c and FPG relative to placebo (P<0.001) (Figure 3 and Table 3). Attainment of HbA1c ≤7% was seen in 17% of sitagliptin-treated subjects and 5% of placebo-treated subjects (P<0.001). Sitagliptin was generally well tolerated; a modest though statistically significant increase in body weight from baseline was noted (Table 3). Incidence of hypoglycemic events was higher in the sitagliptin group, but the rate was comparable to those reported in other studies of sulfonylurea-containing oral combination thera-

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**Figure 3** Glycemic effect of incretin therapeutics combined with a sulfonylurea drug. HbA1c = hemoglobin A1c. *Not currently approved for use in the United States or European Union; †adjusted value; ‡significant vs. placebo; §significant between-group differences vs. placebo; ‡not currently approved for use in United States. (Adapted from *Diabet Med,* *Diabetes Care,* and *Diabetes Obes Metab*.)
The dosages of thiazolidinedione (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) and metformin were constant throughout the study. At 16 weeks, the addition of exenatide to treatment regimens resulted in significant reductions in HbA1c, FPG, and body weight compared with placebo ($P < 0.001$ for all endpoints) (Figure 4 and Table 4). In the exenatide-treated cohort, 62% achieved HbA1c ≤7%, compared with 16% of patients in the placebo add-on group ($P < 0.001$). The most frequent adverse event was nausea, occurring in 39.7% of patients treated with exenatide and 15.2% of patients in the placebo group. Vomiting occurred more frequently in the treatment group (13.2%) than in patients who received the placebo injections (0.9%). The incidence of hypoglycemia was low and similar across both groups of patients. No cases of severe hypoglycemia were reported.

The addition of sitagliptin 100 mg daily to the treatment of patients with type 2 diabetes failing monotherapy with pioglitazone (30 or 45 mg/day) was evaluated in a 24-week, placebo-controlled trial (N = 353) (Table 4 and Figure 4). Sitagliptin significantly reduced mean HbA1c, reduced FPG, and increased the number of patients who achieved the HbA1c goal of ≤7% (45% vs. 23%, $P < 0.001$ for all endpoints) (Figure 4 and Table 4). Incidence of hypoglycemia was low and not significantly different across comparator groups. There was no significant change in body weight compared with placebo in patients treated with sitagliptin.

Garber and colleagues assessed the utility of adding exenatide to the regimen of patients with type 2 diabetes failing monotherapy with sulfonylurea drug alone. This randomized, double-blind, multicenter study (N = 515) was conducted over a 24-week period using vildagliptin 50 mg, given once or twice daily, versus placebo. The adjusted mean change in HbA1c was significantly superior with both vildagliptin doses compared with placebo ($P < 0.001$) (Figure 3); however, no significant differences in the adjusted mean change in FPG were observed (Table 3). Significantly greater proportions of patients receiving vildagliptin 50 mg daily (21.2%) and 50 mg twice daily (24.8%) achieved HbA1c <7% compared with placebo (12%). Body weight increased significantly in patients receiving vildagliptin 50 mg twice daily versus placebo ($P < 0.001$); change in weight was similar for the vildagliptin 50-mg daily group and placebo (Table 3). The overall incidence of adverse events was similar in all treatment groups. No dose-related adverse effects were observed in the vildagliptin-treated patients.

**EFFICACY OF INCRETIN-BASED THERAPIES IN PATIENTS WHEN COMBINED WITH A THIAZOLIDINEDIONE**

Zinman and colleagues assessed the utility of adding exenatide to the regimen of patients with type 2 diabetes (N = 233) poorly controlled on a thiazolidinedione (with or without metformin) in a placebo run-in, randomized, double-blind, placebo-controlled trial. Patients were randomized to twice-daily administration of exenatide 10 μg or placebo. The dosages of thiazolidinedione (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) and metformin were constant throughout the study. At 16 weeks, the addition of exenatide to treatment regimens resulted in significant reductions in HbA1c, FPG, and body weight compared with placebo ($P < 0.001$ for all endpoints) (Figure 4 and Table 4). In the exenatide-treated cohort, 62% achieved HbA1c ≤7%, compared with 16% of patients in the placebo add-on group ($P < 0.001$). The most frequent adverse event was nausea, occurring in 39.7% of patients treated with exenatide and 15.2% of patients in the placebo group. Vomiting occurred more frequently in the treatment group (13.2%) than in patients who received the placebo injections (0.9%). The incidence of hypoglycemia was low and similar across both groups of patients. No cases of severe hypoglycemia were reported.

The addition of sitagliptin 100 mg daily to the treatment of patients with type 2 diabetes failing monotherapy with pioglitazone (30 or 45 mg/day) was evaluated in a 24-week, placebo-controlled trial (N = 353) (Table 4 and Figure 4). Sitagliptin significantly reduced mean HbA1c, reduced FPG, and increased the number of patients who achieved the HbA1c goal of ≤7% (45% vs. 23%, $P < 0.001$ for all endpoints) (Figure 4 and Table 4). Incidence of hypoglycemia was low and not significantly different across comparator groups. There was no significant change in body weight compared with placebo in patients treated with sitagliptin.

Garber and colleagues assessed the utility of adding exenatide to the regimen of patients with type 2 diabetes failing monotherapy with sulfonylurea drug alone. This randomized, double-blind, multicenter study (N = 515) was conducted over a 24-week period using vildagliptin 50 mg, given once or twice daily, versus placebo. The adjusted mean change in HbA1c was significantly superior with both vildagliptin doses compared with placebo ($P < 0.001$) (Figure 3); however, no significant differences in the adjusted mean change in FPG were observed (Table 3). Significantly greater proportions of patients receiving vildagliptin 50 mg daily (21.2%) and 50 mg twice daily (24.8%) achieved HbA1c <7% compared with placebo (12%). Body weight increased significantly in patients receiving vildagliptin 50 mg twice daily versus placebo ($P < 0.001$); change in weight was similar for the vildagliptin 50-mg daily group and placebo (Table 3). The overall incidence of adverse events was similar in all treatment groups. No dose-related adverse effects were observed in the vildagliptin-treated patients.

**EFFICACY OF INCRETIN-BASED THERAPIES IN COMBINATION WITH TWO ORAL AGENTS**

Kendall and colleagues evaluated the additive effect of exenatide in a 30-week, double-blind, placebo-controlled study performed in 733 patients unable to achieve glycemic control with a combination of metformin and a sulfonylurea. Participants were randomized to exenatide 5 μg, exenatide 10 μg, or placebo in addition to their oral agents. At 30 weeks, mean adjusted HbA1c, FPG, and body weight were significantly reduced in both exenatide groups relative to placebo ($P < 0.0001$ for HbA1c and FPG; $P < 0.01$ for weight) (Figure 5 and Table 5). Exenatide-treated patients were more likely to achieve a target HbA1c of ≤7% than were patients given placebo (34% with exenatide 10 μg and 27% with exenatide 5 μg versus 9% with placebo). Nausea was the most common adverse event in the exenatide-treated patients. The incidence of mild-to-moderate
hypoglycemia was 28% with exenatide 10 μg, 19% with exenatide 5 μg, and 13% with placebo.\textsuperscript{37}

A 52-week, open-label, noninferiority trial described \( \text{HbA}_1c \) reductions with exenatide 10 μg similar to those observed with biphasic insulin aspart 70/30 (Figure 5). Both exenatide- and premixed insulin–treated patients exhibited significant reductions in fasting serum blood glucose values from baseline \( (P < 0.001) \) (Table 5). On average, exenatide–treated patients experienced a decline in body weight, while those patients treated with premixed insulin gained weight,

\textbf{Table 4}  
\textbf{Fasting Glucose and Weight Reduction of Incretin Therapeutics in Combination with Thiazolidinedione}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Baseline Fasting Serum Glucose (mg/dL)*</th>
<th>( \Delta ) Fasting Serum Glucose (mg/dL)*</th>
<th>Baseline Weight (kg)</th>
<th>( \Delta ) Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide\textsuperscript{33}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 μg bid</td>
<td>165</td>
<td>(-29 (P &lt; 0.001)^\dagger)</td>
<td>97.53</td>
<td>(-1.75 (P &lt; 0.001)^\ddagger)</td>
</tr>
<tr>
<td>Placebo</td>
<td>159</td>
<td>(+1.8)</td>
<td>96.75</td>
<td>(-0.24)</td>
</tr>
<tr>
<td>Sitagliptin\textsuperscript{34}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg qd</td>
<td>168</td>
<td>(-16.7 (P &lt; 0.001)^\dagger)</td>
<td>90.9</td>
<td>(+1.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>165</td>
<td>(+1)</td>
<td>86.4</td>
<td>(+1.5)</td>
</tr>
<tr>
<td>Vildagliptin\textsuperscript{35}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg qd (+PG 45 mg qd)</td>
<td>186</td>
<td>(-14)</td>
<td>—</td>
<td>(+1.5 (P = 0.849)^\dagger)</td>
</tr>
<tr>
<td>100 mg qd (+PG 45 mg qd)</td>
<td>180</td>
<td>(-20)</td>
<td>—</td>
<td>(+2.7 (P = 0.003)^\dagger)</td>
</tr>
<tr>
<td>Placebo</td>
<td>182</td>
<td>(-9)</td>
<td>—</td>
<td>(+1.4)</td>
</tr>
</tbody>
</table>

\( PG = \) pioglitazone.  
*1 mg/dL = 0.5551 mmol/L.  
\( ^\dagger\)Significance vs. placebo.  
\( ^\ddagger\)Significance vs. baseline.  
(Adapted from Ann Intern Med,\textsuperscript{33} Clin Ther,\textsuperscript{34} and Diabetes Obes Metab.\textsuperscript{35,36})

Figure 4  
Glycemic effect of incretin therapeutics combined with a thiazolidinedione. \( \text{HbA}_1c = \) hemoglobin A₁c.  
*Not currently approved for use in the United States;  
\( ^\dagger\)significance in the intent-to-treat sample;  
\( ^\ddagger\)significant vs. baseline;  
\( ^\ddagger\)significant vs. placebo.  
(Adapted from Ann Intern Med,\textsuperscript{33} Clin Ther,\textsuperscript{34} and Diabetes Obes Metab.\textsuperscript{35,36})
resulting in a statistically significant between-group difference at the 52-week endpoint ($P < 0.001$) (Table 5). The incidence of gastrointestinal side effects was higher in the exenatide group, with nausea (33%) and vomiting (15%) the most common reported adverse events. The rate of hypoglycemia was similar in both treatment groups, and no severe hypoglycemic events were reported.38

Heine and coworkers39 conducted a 26-week, multicenter, randomized trial comparing the addition of exenatide or insulin glargine in 551 patients with type 2 diabetes that was controlled suboptimally with metformin and a sulfonylurea drug. At study end, the adjusted mean value of HbA1c was similarly reduced from baseline in both treatment groups. Proportions of patients achieving HbA1c $< 7\%$ were also similar (46% for exenatide and 48% for insulin glargine). Reductions in FPG levels were significantly greater in patients treated with insulin glargine ($P < 0.001$). Exenatide was associated with weight reduction, insulin glargine with weight gain; the between-group weight change was statistically significant ($P < 0.0001$) (Table 5). The most common adverse events in the exenatide-treated group were nausea (57.1%) and vomiting (17.4%). The incidence of nausea, vomiting, and diarrhea in the exenatide-treated group was statistically significantly greater compared with the insulin glargine–treated group ($P < 0.001$). The overall rate of hypoglycemia was similar in both treatment groups (7.3 events per patient-year in the exenatide group compared with 6.3 events per patient-year in the insulin glargine group).39

Russell-Jones and colleagues40 performed a 26-week trial to compare liraglutide and insulin glargine when added to metformin plus glimepiride. Patients ($N = 581$) were randomized to liraglutide 1.8 mg/day, insulin glargine (titrated in a regimen based on the AT-LANTUS protocol),42 or placebo; liraglutide dosing was blinded, whereas insulin glargine therapy was open label. Liraglutide reduced HbA1c to a significantly greater degree compared with insulin glargine or placebo ($P = 0.0015$ and $P < 0.0001$, respectively) (Figure 5). Achievement of HbA1c $\leq 7\%$ was also significantly superior with liraglutide (53% of subjects) compared with glargine (46%; $P = 0.0139$) and placebo (15%; $P < 0.0001$). Liraglutide and glargine reduced FPG by similar amounts. Body weight was significantly reduced
by liraglutide versus both metformin plus sulfonylurea (\(P = 0.0001\)) or versus insulin glargine in combination with metformin plus sulfonylurea (\(P < 0.0001\)) (Table 5). Gastrointestinal symptoms were the most frequent adverse events in patients treated with liraglutide; 14% of subjects in this group reported nausea. The incidence of nausea in the liraglutide group was initially 5% to 7% of subjects. Five liraglutide-treated patients (2.2%) and no patients in the other groups experienced major hypoglycemic episodes. The incidence of minor hypoglycemia was similar with liraglutide (27%), glargine (29%), and placebo (17%).40

A 26-week double-blind study evaluated liraglutide in combination with metformin and a thiazolidinedione. Subjects (N = 533) were randomized to liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, or placebo in addition to metformin plus rosiglitazone. Liraglutide 1.2 mg and 1.8 mg significantly reduced HbA1c, FPG, and weight compared with placebo (\(P < 0.0001\) for all endpoints) (Figure 5 and Table 5). The proportion of patients reaching HbA1c ≤7% was significantly greater with 1.2 mg (58%) and 1.8 mg (54%) compared with placebo (28%) (\(P < 0.0001\) for both doses of liraglutide). Nausea occurred in 29.4% of patients treated with 1.2 mg and 39.9% of patients treated with liraglutide 1.8 mg, compared with 8.6% of placebo-treated patients. Nausea incidence in the liraglutide groups decreased to the same level as placebo by week 16 of the study. No major hypoglycemic episodes were reported. The incidence of minor hypoglycemia with liraglutide 1.8 mg was significantly higher than the incidence with placebo, but rates in all groups were low: liraglutide 1.2 mg (0.38 events per year), liraglutide 1.8 mg (0.64 events per year), and placebo (0.17 events per year).51

### EFFICACY OF INCRETIN-BASED THERAPIES IN PATIENTS TREATED WITH INSULIN

Fonseca and colleagues43 assessed the efficacy and tolerability of vildagliptin added to insulin therapy in patients with inadequately controlled type 2 diabetes. In the 24-week, double-blind, randomized, placebo-controlled trial, patients received vildagliptin 50 mg bid (n = 144) or placebo (n = 152) in addition to insulin. The mean insulin dose in the combined cohort was 82 U/day. In patients receiving vildagliptin, the reduction in HbA1c from baseline was significantly greater than with placebo (\(P = 0.010\)). Changes in FPG and body weight did not demonstrate statistically significant between-group differences. Rates of hypoglycemia and severe hypoglycemia were lower in the vildagliptin compared with placebo (\(P < 0.001\)). The overall frequency of adverse events was similar in both groups, as was the percentage of serious adverse events: vildagliptin (8.3%) and placebo (9.2%).43

### SAFETY OF INCRETIN THERAPIES

The incidence of gastrointestinal side effects has been relatively high in studies assessing exenatide, particularly at the higher 10-μg dose. In the sulfonylurea add-on trial, nausea was reported in 51% of patients who received the 10 μg bid dosage, compared with only 7% of those who received sulfonylurea alone.30 Nausea was more common when exenatide 10 μg bid was used with metformin (45%
vs. 23%) as well as when that dose was combined with metformin plus a sulfonylurea (48.5% vs. 20.6%). In general, the incidence of nausea declined with longer duration of treatment. In phase 3 trials of liraglutide, 1.8-mg/day dosage was associated with nausea rates of between 7% and 40%, compared with rates of 2% to 9% in the placebo arms. The incidence of nausea typically declined over the first 4 weeks of treatment.

Both exenatide and exenatide-LAR appear to elicit an immune response. Detectable antibodies to exenatide have developed in a substantial number of clinical trial patients (approximately 40% to 50%). Rate of antibody formation appears to be higher with exenatide-LAR, occurring in 74% of patients in a recent phase 3 trial, and in 67% in a phase 2 trial. High-titer (≥1/625) antibody levels were detected in 24% of patients to whom exenatide-LAR was administered. In the majority of patients, antibodies have not been shown to influence glycemic response in the referenced studies. However, in the proportion of patients (~6%) who developed high-titer antibodies, approximately half (3%) showed evidence of attenuated glycemic response. In the exenatide-LAR phase 3 studies referenced above, glycemic response appeared to be attenuated (HbA1c reduction of ~1.4%) in the 24% of patients who developed high-titer antibodies compared with the response (HbA1c reduction of ~1.9%) in patients without antibodies. Liraglutide’s nearly identical homology to native GLP-1 has meant that reports of antibodies in clinical trials have occurred at a much lower rate (0% to 13%) than has been observed with exenatide.

Cases of acute pancreatitis in patients taking exenatide have been reported to the FDA, which prompted a request for a warning label instructing prescribers to be vigilant for signs and symptoms of pancreatitis. During clinical development, however, the incidence of acute pancreatitis in patients treated with exenatide (1.7 cases per 1,000 subject-years) was lower than the incidence observed in comparator groups treated with placebo (3.0 cases per 1,000 subject-years) or insulin (2.0 cases per 1,000 subject years). Given that patients with type 2 diabetes have as much as a 3-fold increased risk of pancreatitis compared with the general population, it is not possible to determine at this time whether the reported cases are attributable to exenatide or to preexisting elevated risk.

DPP-4 inhibitors have proved to be generally safe and well tolerated in clinical trials. Sitagliptin is primarily excreted via renal elimination; thus the dosage must be adjusted in patients with moderate-to-severe renal insufficiency or end-stage renal disease. Hypoglycemia and gastrointestinal adverse events appear to be infrequent. A meta-analysis by Amori and colleagues reported that DPP-4 inhibitors may be associated with a 1.2-fold increased risk of infection for nasopharyngitis, a 1.5-fold increased risk for urinary tract infection, and a 1.4-fold increased risk for frequency of headache.

In postmarketing studies of sitagliptin, severe skin reactions, including some cases of Stevens-Johnson syndrome, have been reported. As most trials with DPP-4 inhibitors are of 30 weeks duration, longer follow-up is needed to establish the long-term safety of these agents.

SUMMARY

Both GLP-1 receptor agonists and DPP-4 inhibitors provide unique benefits with different modes of action that complement and extend the present therapeutic armamentarium for the treatment of type 2 diabetes. DPP-4 inhibitors are effective, well-tolerated, weight-neutral oral agents. Because of their ease of use for both patients and providers, DPP-4 inhibitors will play an increasingly important role in the treatment of type 2 diabetes. While the efficacy of exenatide is limited by its relatively short half-life and minor effects on fasting glucose levels, longer-acting GLP-1 receptor agonists, such as liraglutide, exenatide-LAR, and other molecules in development have more robust effects on fasting glucose levels and appear to offer superior efficacy to exenatide and most oral agents. In addition, an important attribute of members of this class is their ability to promote weight loss. Despite their proven benefits, GLP-1 receptor agonists must be administered subcutaneously; therefore, healthcare providers should be prepared to address any potential patient barriers to injection.

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Matthew P. Gilbert, DO, MPH, reports no relationships to disclose with any manufacturer of a product or device discussed in this supplement.

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