REVIEW

A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond

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Abstract

The prevalence of type 2 diabetes is increasing at an astounding rate. Many of the agents used to treat type 2 diabetes have undesirable adverse effects of hypoglycemia and weight gain. Glucagon-like peptide-1 (GLP-1) receptor agonists represent a unique approach to the treatment of diabetes, with benefits extending outside glucose control, including positive effects on weight, blood pressure, cholesterol levels, and beta-cell function. They mimic the effects of the incretin hormone GLP-1, which is released from the intestine in response to food intake. Their effects include increasing insulin secretion, decreasing glucagon release, increasing satiety, and slowing gastric emptying. There are currently four approved GLP-1 receptor agonists in the United States: exenatide, liraglutide, albiglutide, and dulaglutide. A fifth agent, lixisenatide, is available in Europe. There are important pharmacodynamic, pharmacokinetic, and clinical differences of each agent. The most common adverse effects seen with GLP-1 therapy include nausea, vomiting, and injection-site reactions. Other warnings and precautions include pancreatitis and thyroid cell carcinomas. GLP-1 receptor agonists are an innovative and effective option to improve blood glucose control, with other potential benefits of preserving beta-cell function, weight loss, and increasing insulin sensitivity. Once-weekly formulations may also improve patient adherence. Overall, these are effective agents for patients with type 2 diabetes, who are either uncontrolled on metformin or intolerant to metformin.

Keywords: type 2 diabetes mellitus, glucagon-like peptide-1 receptor agonist, subcutaneous, albiglutide, dulaglutide, liraglutide, exenatide, beta cell, insulin sensitivity, weight loss.

Abbreviation: GLP-1, Glucagon-like peptide-1.

Introduction

An astounding 387 million people worldwide are diagnosed with type 2 diabetes and are subject to the myriad of diabetes-related complications that can ensue, including cardiovascular issues, nephropathy, neuropathy, and retinopathy, among other organ disturbances [1]. While the American Diabetes Association recommends metformin as first-line therapy due to its efficacy in reducing hemoglobin A1C, widespread availability, safety, and tolerability, a single agent is often not sufficient to bring a patient's blood glucose level to meet the target [2]. Beyond initial treatment with metformin, the American Diabetes Association and European Association for the Study of Diabetes consider a multitude of other agents as potential second-line options, including sulfonylureas, thiazolidinediones, insulin, and dipeptidyl peptidase-4 inhibitors (DPP-4) [3]. While all agents in the diabetes armamentarium provide patients the benefit of glucose reduction, numerous options, including sulfonylureas, thiazolidinediones, and insulin, have undesirable effects, which include weight gain and hypoglycemia, potentially limiting their overall use in some patient populations. Additionally, the therapeutic longevity of some agents, including sulfonylureas and meglitinides, may be shortened due to their mechanism of action of enhancing insulin secretion, and the natural beta-cell burnout that ensues in long-standing type 2 diabetes [4]. Glucagon-like peptide-1 (GLP-1) receptor agonists offer a unique and innovative treatment advancement to the management of type 2 diabetes mellitus. They demonstrate benefits not only in blood glucose control but potentially preserve beta-cell function and improve other diabetes-related co-morbid conditions, such as hypertension, hyperlipidemia, and obesity [5–7]. This article will discuss the various GLP-1 receptor agonists available on the market, specifically focusing on efficacy, safety, and clinical differences among the different agents; describe the adverse effects and toxicities seen with these agents; and finally, discuss potential benefits in addition to glucose lowering in type 2 diabetes.

Incretin hormones and diabetes

Many medications utilized in the treatment of diabetes target cornerstone hormonal alterations that result in glucose defects, which include deficiencies in insulin secretion, alterations in glucagon secretion, and insulin resistance, all of which contribute to hyperglycemia. The incretin hormones also serve as a potential therapeutic target. The incretin effect describes the phenomenon that individuals have greater secretion of insulin following oral glucose challenges as opposed to intravenous glucose, suggesting that gastrointestinal hormones are responsible for a portion of insulin secretion [8]. Several studies have demonstrated that this rise in insulin secretion is deficient in individuals with diabetes, further augmenting high glucose concentrations [9]. In one study performed by Toft and colleagues, 59 individuals diagnosed with type 2 diabetes mellitus were compared to 33 control subjects without any evidence of impaired glucose tolerance, as well as with a group of participants who were recently diagnosed with impaired glucose tolerance. After an overnight fast, individuals were given a standardized meal, and concentrations of incretin hormones, insulin, glucagon, and C-peptide, among other parameters, were measured. In terms of incretin hormones, patients diagnosed with type 2 diabetes had significantly lower GLP-1 concentrations stimulated by caloric intake when compared to individuals without diabetes. Individuals with pre-diabetes had GLP-1 concentrations that were higher than patients with diabetes, but less than those who did not have evidence of the disease, potentially suggesting that deficiencies in the incretin pathway may begin before a clinical diagnosis of diabetes. Interestingly, the secretion of GLP-1 and gastric-inhibitory peptide (GIP), another incretin hormone, had no bearing on each other [9].

GLP-1 and GIP

Although the incretin hormones have multiple effects that reduce glucose concentrations, GLP-1 offers significantly more benefits compared to GIP [10,11]. Upon the ingestion of food, concentrations of both GLP-1 and GIP increase substantially [10]. Both GIP and GLP-1 appear to increase insulin secretion in response to food intake and increase beta-cell mass in animal models, an attractive feature since at diagnosis of type 2 diabetes, approximately 50% of beta-cell mass is lost [11,12]. GLP-1, however, also decreases glucagon secretion, decreases hepatic gluconeogenesis, improves insulin sensitivity, and delays gastric emptying, potentially promoting central satiety and reducing overall caloric intake [10]. In patients with type 2 diabetes, the promotion of central satiety is an attractive feature, as weight loss is an essential goal in diabetes self-management. In other clinical trials, the addition of GIP to GLP-1 infusion did not augment the insulin secretory response of GLP-1, but instead increased glucose concentrations due to a significant antagonistic effect on glucagon suppression [13]. Because GLP-1 offers more therapeutic advantages in

the treatment of diabetes, the focus of leveraging the incretin system for the treatment of diabetes has centered on GLP-1.

The usefulness of endogenous incretin hormones in glucose homeostasis is limited by rapid degradation by the DPP-4 enzyme, resulting in a half-life of GLP-1 of approximately 2 minutes [14]. Continuous infusion of exogenously administered GLP-1 receptor agonists has proven to be successful in overcoming the short half-life and results in a decrease in blood glucose concentrations [15]. In one study by Zander and colleagues, 20 patients with type 2 diabetes were randomized to receive either a subcutaneous continuous infusion of normal saline or a subcutaneous continuous infusion of GLP-1 for a period of 6 weeks. Assessments were attained on GLP-1 concentrations, insulin, glucagon, and C-peptide concentrations, hemoglobin A1C, and body weight, in addition to self-assessed perceptions of hunger and satiety. At the conclusion of the study, individuals who were randomized to receive subcutaneous GLP-1 infusion had significantly elevated concentrations of GLP-1 compared to those who received saline ($p<0.0001$). Individuals who received GLP-1 also demonstrated significant falls in fasting and postprandial glucose ($p<0.0001$), improved beta-cell function ($p=0.003$), slowed gastric emptying ($p=0.014$), and decreased insulin resistance ($p=0.003$). Individuals randomized to GLP-1 infusion also reported positive benefits of satiety, fullness, and perceived food intake, with a steady weight loss observed throughout the study [15]. This study supported the benefits of GLP-1 receptor agonists in the management of blood glucose, yet was limited by the administration route, since continuous infusion is not a practical approach to the outpatient management of diabetes. This led to more extensive investigation on how to overcome the short half-life of GLP-1 to take advantage of the multimodal benefits offered in patients with diabetes. In addition to the short half-life, an additional challenge to the widespread use of incretin-based therapies is that their peptide-based structure limits oral administration. Due to rapid degradation by gastrointestinal enzymes, they are currently only administered through the subcutaneous route [16].

Pharmacologic profiles, safety, and efficacy of approved agents

Exenatide pharmacology

The first GLP-1 receptor agonist was introduced in the market in 2005. Exenatide BID (Byetta®) [17] is derived from the saliva of the Gila monster, and has 53% homology to native GLP-1 [18]. Because of its structural similarity to native GLP-1, exenatide is able to bind to the GLP-1 receptor *in vivo*, and results in glucose-dependent insulin secretion, essentially restoring the first-phase insulin response [17]—which is often impaired in patients with type 2 diabetes. Exenatide BID is indicated as an adjunct to diet and exercise in patients diagnosed with type 2 diabetes, in the United States and the European Union.

It can be utilized either as monotherapy or in conjunction with other treatment options, including basal insulin. After injection, exenatide levels can be measured for approximately 10 hours, although peak levels are achieved at 2.1 hours after injection. Because exenatide restores the first-phase insulin response, injections should be administered prior to meal times, and not after eating [17]. Specifically, exenatide is indicated as a twice-daily injection, administered within the 60-minute window prior to eating the two main meals of the day. To minimize the potential risk of hypoglycemia, each injection should be given at least 6 hours apart. Initially all patients should be started on the 5 μg dose injection to increase tolerability. After a period of 1 month, patients may be titrated to the 10 μg dose [17], as there appears to be a dose-dependent effect on glucose concentrations [19]. In patients who are unable to tolerate exenatide due to nausea and vomiting, common adverse effects of exenatide therapy, the 5 μg dose appears also to be effective at reducing overall hemoglobin A1C [17,19].

Exenatide clinical trials

Exenatide BID demonstrated efficacy in improving glycemic control in a 30-week study of 336 patients who were already receiving background metformin therapy. Patients who were on at least 1500 mg of metformin daily were randomized to receive a placebo, exenatide 5 μg twice daily for the entire study period or exenatide 5 μg twice daily titrated to 10 μg twice daily after 4 weeks. At the conclusion of the study, individuals randomized to the 10 μg twice-daily group experienced a hemoglobin A1C reduction of approximately 0.78%, while those who received 5 μg twice daily achieved approximate A1C reductions of 0.4%, both of which were statistically significant compared with placebo ($p<0.002$). Additionally, patients who received either dose of exenatide therapy experienced a statistically significant effect on weight loss, which was dose dependent. The weight loss exhibited with exenatide therapy was consistent with the known effect of the agent to reduce overall caloric intake. The most frequently seen adverse effects with exenatide in this study included nausea, vomiting, and hypoglycemia (which did not differ among treatment arms). This study demonstrated that exenatide can provide an additive treatment effect to patients who are unable to achieve glycemic control with sufficient doses of metformin therapy [19].

In a number of clinical trials, exenatide BID demonstrated superiority over commonly utilized diabetes treatments [20,21]. In one study, exenatide demonstrated superiority over glimepiride in reducing hemoglobin A1C [20]. Patients who were unable to achieve glycemic targets on metformin monotherapy were randomized to receive either exenatide (n=515) or glimepiride (n=514). At the conclusion of the study, there was a statistically significant increase in treatment failure among patients who received glimepiride (41% in exenatide group *vs* 54% in glimepiride group, HR=0.748, p=0.002). Additionally, a significantly larger percentage of

patients achieved their hemoglobin A1C targets when treated with exenatide. Weight loss was observed with exenatide, and although hypoglycemia occurred to a significantly larger extent in patients treated with sulfonylurea, treatment discontinuation within the first 6 months was more frequently associated with exenatide; gastrointestinal complaints were the primary cause [20].

Dipeptidyl-peptidase inhibitors offer another novel alternative to traditional diabetes treatment regimens. They enhance GLP-1 activity by inhibiting the DPP-4 enzyme [16]. Nonetheless, this is done less effectively than with GLP-1 receptor agonists [21]. In one study that evaluated the effects of exenatide compared with sitagliptin on glycemic control, exenatide demonstrated superiority over sitagliptin in reducing glucose concentrations. Patients with type 2 diabetes mellitus who were also taking metformin received sitagliptin 100 mg daily for 2 weeks, or exenatide 5 μg twice daily for 1 week, titrated to exenatide 10 μg twice daily for 1 week. After the 2-week period, patients were crossed-over to the other arm of the study. After 2 weeks of therapy, postprandial glucose concentrations were significantly lower with exenatide ($p<0.00001$). Additionally, treatment with exenatide was associated with significantly increased insulin secretion, reduced postprandial glucagon secretion, and reduced caloric intake (all $p<0.05$). Postprandial glucose was increased by 73 mg/dL when switching from exenatide to sitagliptin, while switching from sitagliptin to exenatide reduced postprandial glucose by approximately 76 mg/dL. Although this study was limited by its short duration, it demonstrated superiority of GLP-1 receptor agonists over DPP-4 inhibitors in glycemic control [21].

Liraglutide pharmacology

Liraglutide (Victoza®), the second GLP-1 receptor agonist introduced in the United States market, received its initial FDA approval in 2010 as an adjunct to diet and exercise in patients with type 2 diabetes. However, liraglutide is not recommended as a first-line agent and should not be utilized as monotherapy [22]. Liraglutide has 97% homology to native GLP-1 [22] and exhibits greater similarity than exenatide [22]. Liraglutide's prolonged half-life of 13.1 hours is due to delayed absorption and considerable resistance against DPP-4 degradation [22]. This is primarily a result of a fatty acid substitution in the structure that results in albumin bonding, which extends the duration of action [23]. Therefore, liraglutide is suitable for once-daily administration without regards to meals [22]. After injection, liraglutide binds to the GLP-1 receptor and results in increases in insulin secretion and reductions in postprandial glucagon [22]. In comparison to exenatide, liraglutide appears to have a greater effect on reducing hemoglobin A1C [7], presumably due to its longer half-life and greater effect on fasting glucose concentrations. Liraglutide should be initiated at a dose of 0.6 mg once daily for 1 week and then titrated to 1.2 mg daily. If the 1.2 mg dose does not achieve glycemic goals, the dose can be further increased to 1.8 mg daily.

Patients should be counseled that the initial dose of 0.6 mg daily is ineffective for glycemic control, and is only initiated to maximize patient tolerance to the potential gastrointestinal effects of the medication [22].

Liraglutide clinical trials

The LEAD-6 clinical trial was a 26-week multinational trial that evaluated liraglutide's effects on glucose concentrations compared with exenatide twice daily [7]. All individuals had type 2 diabetes with hemoglobin A1C ranges from 7 to 11% and had a stable background therapy of metformin and/or a sulfonylurea. Two-hundred thirty-three patients were randomized to receive liraglutide 1.8 mg after a 2-week dose titration period (0.6 mg × 1 week, then 1.2 mg × 1 week, finally titrated to 1.8 mg daily). In contrast, 231 patients were randomized to receive exenatide 5 μg twice daily, titrated to a goal dose of 10 μg twice daily after 4 weeks. After this titration period, dose reduction was not allowed of either agent, and if therapy was not tolerated, participants were removed from the trial. After a period of 26 weeks, individuals who were treated with liraglutide had a statistically significant greater reduction in their hemoglobin A1C over patients in the exenatide group (–1.12% for liraglutide patients vs –0.79% for exenatide patients). Additionally, a larger proportion of patients in the liraglutide treatment arm achieved their goal hemoglobin A1C target of 7% compared to exenatide (54 vs 43%). With respect to their durations of action, liraglutide was significantly better at reducing fasting blood glucose concentrations, while exenatide was superior at reducing postprandial glucose concentrations (p<0.0001 for both parameters). Weight loss did not differ significantly between groups, and patients experienced an average 3 kg weight reduction. Nausea occurred at a similar rate in both treatment arms. However, individuals treated with liraglutide had resolution of their symptoms sooner than those treated with exenatide. The majority of liraglutide-induced nausea patients were symptom free by week 6, while the same proportion of the exenatide-treated group was not symptom free until week 22 [7]. Interestingly, although treatment satisfaction was higher with liraglutide, there were more severe adverse effects associated with liraglutide therapy [7].

In a 14-week extension trial of LEAD-6, 187 patients who received exenatide therapy during the initial 26-week period were switched to liraglutide 1.8 mg daily, and were followed with 202 patients who continued their initial liraglutide regimen. After 14 weeks of therapy, individuals who were switched from exenatide to liraglutide experienced a statistically significant further reduction in their hemoglobin A1C of 0.32%. Liraglutide patients continued to experience reductions as well, of approximately –0.1%, although this was not statistically significant [24]. These changes in hemoglobin A1C derived from switching therapies are most likely due to prolonged GLP-1 exposure of the once-daily formulation of liraglutide, over the short diurnal exposure of exenatide

therapy. In this trial, patients switched therapy without any significant increase in adverse effects [24].

In another clinical trial that evaluated the effects of liraglutide compared with insulin glargine in patients treated with background metformin and/or sulfonylureas, liraglutide reduced hemoglobin A1C to a significantly greater extent when compared to insulin glargine (–1.33 vs –1.01% for liraglutide and glargine, respectively) [25]. All patients received a dose of liraglutide 1.8 mg daily (after the initial 2-week dose escalation period), and insulin glargine, self-titrated according to an algorithm, to achieve glycemic control. After 26 weeks, individuals who received the GLP-1 receptor agonist experienced greater reductions in hemoglobin A1C. Additionally, a larger proportion of patients achieved their blood glucose goals, and GLP-1 receptor agonist treatment was associated with clinically significant weight loss, while individuals who were randomized to receive insulin glargine experienced weight gain. Liraglutide was associated with mild to moderate gastrointestinal effects, although serious adverse effects were reported to a higher degree with insulin glargine treatment. Rates of hypoglycemia did not differ between the two treatment arms. Although liraglutide was superior to insulin in reducing hemoglobin A1C in this trial, patients self-titrating their insulin dose may have potentially limited the aggressiveness of dosing [25]. Utilizing a more intensive treat-to-target approach may allow for greater hemoglobin A1C reductions in the insulin glargine arm. Nonetheless, the trial demonstrated positive benefits of liraglutide on body weight, beta-cell function, and cardiovascular markers, such as blood pressure, which should not be underestimated [25].

Exenatide once weekly pharmacology

Introduced in the United States market in 2012, exenatide long-acting release (Bydureon®) was the first once-weekly GLP-1 receptor agonist to receive FDA-approved labeling as adjunctive therapy to diet and exercise for patients with type 2 diabetes [26]. With a pharmacologic composition identical to the exenatide twice daily compound, exenatide once weekly is released into the blood circulation through poly-microsphere delivery over a period of 10 weeks, resulting in its long duration of action. Two concentration peaks can be observed following administration, the initial peak occurring at week 2 due to release of surface-bound exenatide, and the subsequent peak occurring at approximately week 7, which is primarily due to microsphere release of the drug. Steady state concentrations are reached by approximately week 7. Exenatide long-acting release is administered as a 2 mg once-weekly subcutaneous injection and is available through two formulations, one as a single-dose vial that requires patient reconstitution with diluent, and another as a ready-to-use prefilled injection pen [26]. In clinical trials, gastrointestinal adverse effects were declined with the extended release

formulation over the twice-daily composition [6], presumably due to the slow, steady increase in plasma concentrations of the long-acting formulation over twice-daily administration. In trials that have evaluated patient satisfaction, once-weekly formulations of GLP-1 receptor agonists exhibited perceived patient convenience, improved adherence, improved quality of life, and fewer perceptions of burdens of treatment over traditional diabetes agents [27]. Ultimately, this may have great implications on patient adherence and overall clinical outcomes.

Exenatide once weekly clinical trials

Exenatide once weekly was evaluated in a number of clinical trials that compared the once-weekly formulation with exenatide twice daily administration, liraglutide, insulin glargine, and other oral diabetes medications [6,26,28,29]. In a noninferiority trial that occurred over 30 weeks, exenatide 2 mg once weekly was compared to exenatide 10 µg twice daily. Background pharmacologic treatment of metformin, thiazolidinediones, and sulfonylureas, or any combination of the two of these agents was continued [6]. If the patient was receiving a concomitant sulfonylurea, the dose was decreased according to the package insert for exenatide, to reduce the potential for hypoglycemia [26]. At the conclusion of the trial, patients in both arms experienced significant hemoglobin A1C reductions from baseline, although the mean reduction was significantly greater with once-weekly administration (A1C reduction: –1.9% for exenatide once weekly *vs* –1.5% for exenatide BID, *p*=0.0023). Additionally, a greater proportion of patients achieved their hemoglobin A1C targets when treated with the extended formulation. Both treatment arms exhibited clinically significant weight loss, although the difference was not statistically significant. While both treatment arms demonstrated significant reductions in fasting and postprandial glucose from baseline, fasting glucose was decreased to a greater extent with the extended formulation. In contrast, changes in postprandial concentrations were greater with the twice-daily formulation [6]. This is not surprising considering the sustained exposure of the extended formulation compared with the diurnal exposure of the twice-daily product [17,26]. In terms of adverse effects, a greater proportion of patients experienced treatment-related nausea and vomiting with the twice-daily injection, while injection site pruritus occurred more frequently with the extended formulation. Overall, this study demonstrated that while both exenatide formulations exhibited reductions in hemoglobin A1C, the extended release formulation was superior in achieving blood glucose targets, without increasing the risk of hypoglycemia or compromising the benefits of weight loss [6].

In a trial conducted from 2010 to 2011, exenatide once weekly was compared to another FDA-approved GLP-1 receptor agonist, liraglutide. Four hundred sixty-one patients were randomized to receive exenatide once weekly at a dose of 2 mg daily, along with 450 patients who received liraglutide 1.8 mg daily after a 2-week dose escalation period of 26 weeks. Background oral medications were continued, with the exception of alpha-glucosidase inhibitors, rosiglitazone, meglitinides, and DPP-4 inhibitors. After study conclusion, both agents exhibited significant hemoglobin A1C changes from baseline, with the average reduction of –1.48% with liraglutide and –1.28% with exenatide once weekly. The change in hemoglobin A1C was superior in patients taking liraglutide (*p*=0.02) [28]. All patients experienced treatment-related weight loss, although the individuals treated with liraglutide lost more weight compared with the once-weekly formulation of exenatide [28]. This is an interesting finding, considering the extended duration of action of exenatide once weekly when compared to liraglutide [22,26]. Patients treated with liraglutide experienced a significantly greater reduction in their fasting plasma glucose as opposed to individuals treated with exenatide (*p*=0.02), although both groups experienced significant reductions from baseline (*p*<0.0001). A greater percentage of patients experienced an adverse effect with liraglutide, with the most frequently reported being nausea which occurred at a rate of 21% with liraglutide and 9% with exenatide. Additionally, a higher percentage of patients discontinued therapy when treated with liraglutide due to adverse effects. In contrast, exenatide therapy was associated with a higher percentage of serious adverse effects [28].

Treatment with exenatide once weekly was also compared to insulin glargine in a 26-week open label study. Patients were randomized to receive exenatide 2 mg weekly or insulin glargine at an initial dose of 10 units daily, titrated to goal blood with or without a sulfonylurea. Reductions in sulfonylurea dosage occurred if the patient experienced treatment-related hypoglycemia during the study. At study conclusion, the change in baseline hemoglobin A1C was significantly greater with exenatide once weekly when compared to insulin glargine (–1.5% with exenatide once weekly *vs* –1.3% with insulin glargine, treatment difference of –0.16%, *p*=0.017) [29]. Patients treated with insulin glargine had lower fasting glucose concentrations, while those who received GLP-1 therapy had reduced postprandial concentrations [29], consistent with the effects of GLP-1 on satiety, caloric intake, and postprandial glucose excursions [10,13]. Expectedly, patients experienced weight loss with GLP-1 treatment, while those who received insulin therapy experienced a treatment-related weight gain of approximately 1.4 kg. Patients who received exenatide had a higher incidence of adverse effects overall, with the most frequently reported being nausea and vomiting. Hypoglycemia, however, occurred to a greater extent with insulin treatment, especially when patients received concurrent sulfonylureas as background therapy [29].

Because steady state concentrations are not achieved with exenatide once weekly therapy until approximately week 7, clinicians should be aware that cross-titration with other medications may be necessary for the first few weeks of therapy to ensure optimal glycemic control.

Albiglutide pharmacology

In 2014, the second once-weekly GLP-1 receptor agonist, albiglutide (Tanzeum®), received FDA approval for the treatment of type 2 diabetes in patients unable to achieve glycemic targets. Similar to exenatide once weekly, albiglutide is not appropriate as a first-line agent for therapy [30]. Albiglutide's extended duration of action is due to two copies of the amino acid molecule that bind to albumin *in vivo*, resulting in a half-life of approximately 5 days [31]. Albiglutide is administered initially as a 30 mg subcutaneous once-weekly injection without regards to meals. Therapeutic concentrations of albiglutide can be achieved within 3–5 days following initial administration, with steady state concentrations achievable after 28–35 days following initial injection [30,31]. For patients who are unable to achieve their glycemic targets, dose escalation from 30 mg weekly to 50 mg once weekly is appropriate and resulted in a further improvement in glycemic control in clinical trials [30,32].

Albiglutide clinical trials

Albiglutide's efficacy compared with insulin glargine's was evaluated in a 52-week noninferiority trial that enrolled 779 patients. Individuals were randomized to receive either albiglutide 30 mg once weekly, titrated up to a dose of 50 mg if necessary for glycemic control, or insulin glargine 10 units daily, with a treat-to-target approach. At the end of the 1-year treatment period, hemoglobin A1C decreased significantly in both treatment groups, with a reduction of approximately –0.66% with GLP-1 therapy and –0.81% with insulin glargine, and a treatment difference of 0.11% between agents, meeting the criteria for albiglutide noninferiority. Similar to other clinical trials that evaluated a GLP-1 receptor agonist against an insulin comparator, individuals treated with insulin experienced treatment-related weight gain and higher rates of hypoglycemia. The authors concluded that albiglutide is a safe alternative to insulin glargine with the additional benefits of weight loss and without an increase in adverse effects [33].

In a clinical trial comparing albiglutide and liraglutide treatment groups, albiglutide did not meet the criteria for noninferiority when compared to liraglutide, although both treatment groups experienced clinically significant reductions in hemoglobin A1C of approximately –0.78% and –0.99% for albiglutide and liraglutide, respectively. Patients with type 2 diabetes were randomized to receive either albiglutide 30 mg once weekly, which could be escalated to a dose of 50 mg once weekly after 6 weeks, or liraglutide 0.6 mg daily, titrated to the goal dose of 1.8 mg daily after 2 weeks. Interestingly, in this trial, patients could also begin rescue therapy after goal dose of GLP-1 was achieved to further improve glycemic control. Liraglutide therapy was associated with a significantly higher percentage of patients reaching glycemic targets, greater reductions in fasting plasma glucose, and significantly greater weight loss. However, adverse effects, including nausea,

vomiting, and hypoglycemia, occurred at higher rates in the liraglutide treatment arm, except for injection-site reactions which were more frequent with albiglutide. Although in this trial, hemoglobin A1C reduction was not as great with albiglutide when compared to liraglutide, overall, albiglutide was better tolerated. Thus, albiglutide may be an alternative option in patients who cannot tolerate shorter-acting GLP-1 receptor agents due to adverse effects [34].

Dulaglutide pharmacology

In 2014, dulaglutide (Trulicity®), a once-weekly GLP-1 injection, received FDA approval as adjunctive therapy for the management of type 2 diabetes [35]. Administered as a 0.75 mg injection, the dose can be escalated to 1.5 mg once weekly to achieve glycemic targets. Therapeutic concentrations are achieved faster with dulaglutide compared to other once-weekly GLP-1 receptor agonists, within 1–3 days [35], while steady state concentrations occur within 2–4 weeks after administration of the once-weekly injection [35]. Dulaglutide's extended duration of action is due to modified amino acid sequences that resist DPP-4 degradation, as well as the large size of the molecule, reducing renal clearance [36]. Dulaglutide is available in two dosage forms, a prefilled pen syringe ready for injection and a solution for injection that requires reconstitution by the patient prior to administration [35].

Dulaglutide clinical trials

Dulaglutide demonstrated glycemic efficacy in a variety of phase three trials known as the AWARD-studies. Active comparators included exenatide twice daily [37], insulin glargine [38], and liraglutide [39], in conjunction with background therapy that consisted of metformin, pioglitazone, and insulin, depending on the trial. In the AWARD-1 study, which compared dulaglutide with exenatide twice daily, treatment with dulaglutide was superior in reducing hemoglobin A1C compared to exenatide, and patients who were treated with the 1.5 mg dose experienced a dose-related reduction in hemoglobin A1C (–1.51% for dulaglutide 1.5 mg, –1.30% for dulaglutide 0.75 mg, and –0.99% for exenatide twice daily). Weight change from baseline was similar for the dulaglutide 1.5 mg dose when compared to exenatide (–1.30 kg for dulaglutide *vs* –1.07 kg for exenatide, *p*=NS), although patients who were treated with the lower dose of dulaglutide actually experienced a weight gain of 0.20 kg. Gastrointestinal adverse effects were the most commonly reported side effects, and the incidence occurred similarly among the dulaglutide 1.5 mg and exenatide groups. Patients treated with the lower dose of dulaglutide experienced a significantly lower incidence of gastrointestinal complaints (*p*<0.05) [37].

In the AWARD-2 study, dulaglutide at doses of 0.75 mg once weekly and 1.5 mg weekly resulted in a larger reduction in hemoglobin A1C compared to insulin glargine titrated to a goal fasting blood glucose level of <100 mg/dL. This met the criteria

for superiority over insulin glargine for the 1.5 mg dose and noninferiority for the 0.75 mg dose (hemoglobin A1C reduction: –0.9% for dulaglutide 1.5 mg daily, –0.62% for insulin glargine, and –0.59% for dulaglutide 0.75 mg daily). Dulaglutide-treated patients experienced a dose-related weight loss, while patients treated with insulin glargine experienced a weight gain of approximately 1.28 kg over the 72-week treatment period. GLP-1 receptor agonist therapy was associated with improved patient satisfaction when compared to insulin as well [38].

In the AWARD-6 study, 290 patients were randomized to receive dulaglutide 1.5 mg once weekly along with 300 patients who received liraglutide 1.8 mg daily for a treatment duration of 26 weeks. At study conclusion, dulaglutide treatment was associated with a superior reduction in hemoglobin A1C compared to liraglutide (–1.42% for dulaglutide *vs* –1.36% for liraglutide, treatment difference of 0.06%, *p*<0.0001 between treatment groups), meeting the criteria for noninferiority of dulaglutide therapy. Patients treated with liraglutide experienced a significantly greater amount of weight loss compared to dulaglutide (–2.90 kg with dulaglutide *vs* –3.61 kg for liraglutide, *p*<0.001). The most frequently observed adverse effects included gastrointestinal complaints of nausea, vomiting, and diarrhea. There were no significant differences in the incidence of adverse events between the two agents [39].

Lixisenatide

In the European Union, another GLP-1 receptor agonist, lixisenatide (Lyxumia®), is available for the treatment of type 2 diabetes in patients unable to achieve glycemic targets on a traditional diabetes regimen. Indicated as combination therapy with either oral agents or basal insulin, lixisenatide is administered as a 10 μg daily injection titrated to a dose of 20 μg after 2 weeks [40]. Lixisenatide has a half-life of 1.5–3 hours, and when administered as a once-daily injection, it has a positive effect on both the first-phase and second-phase insulin response, providing reductions in both fasting and postprandial glucose concentrations [40,41].

Lixisenatide's efficacy in reducing glucose concentrations was evaluated in a randomized trial that compared lixisenatide once daily to liraglutide once daily. One hundred forty-eight patients were randomized to receive either lixisenatide 10 μg daily titrated to 20 μg after 2 weeks or liraglutide 1.8 mg daily after dose escalation. In comparison to liraglutide, lixisenatide reduced postprandial glucose significantly, although liraglutide was superior at reducing fasting glucose, not surprising considering their respective half-lives. Both lixisenatide and liraglutide lowered hemoglobin A1C significantly from baseline (liraglutide –0.51% *vs* lixisenatide –0.32%; *p*<0.01). Weight loss was similar between the two groups, and treatment was better tolerated with lixisenatide, specifically in regards to gastrointestinal effects. This trial demonstrated that lixisenatide could successfully reduce hemoglobin A1C without increasing gastrointestinal adverse effects or causing hypoglycemia [41].

Global benefits of GLP-1 receptor agonists

Cardiovascular effects

Patients with type 2 diabetes are at increased risk of developing cardiovascular disease and often have other cardiovascular risk factors, including obesity, hypertension, and hyperlipidemia. Therefore, the ideal agent to treat type 2 diabetes would have favorable effects on weight, blood pressure, and lipids [42]. GLP-1 receptor agonists have demonstrated cardioprotective effects in some animal models and clinical studies [6,43]. A retrospective analysis of 39,275 patients indicated that GLP-1 receptor agonists may actually reduce cardiovascular and cerebrovascular events [44]. GLP-1 receptor agonists have been evaluated for weight gain, blood pressure, and lipid parameters, as well as for other cardiovascular events, including arrhythmias, heart failure, myocardial infarction, and death with overall positive benefits [42].

Weight loss

Obesity is associated with increased risk of developing type 2 diabetes, hypertension, and cardiovascular disease. GLP-1 decreases gastrointestinal motility, which increases the time that nutrients can be absorbed. It also increases satiety, increases resting metabolic rate, and lowers plasma concentrations of free fatty acids [45]. In patients with type 2 diabetes, GLP-1 is diminished [9]. In a meta-analysis that included 21 trials and 3395 participants randomly assigned to GLP-1 receptor agonists compared with 3016 participants in various different control groups of different diabetes treatment agents, all trials showed a reduction in weight, which ranged from –0.2 to –7.2 kg. Higher doses of GLP-1 receptor agonists correlated with greater weight loss. Compared with patients on pioglitazone and insulin glargine, who gained weight, the overall weight differences were 4–5 kg [29,46]. Patients taking GLP-1 receptor agonists overall experienced similar weight loss, although there was slight variation depending on the comparator and other trial and patient variables [47]. It is hypothesized that the weight loss benefits may be due to suppressed appetite, reduced body fat, and improved endothelial function (Table 1) [42].

Liraglutide is the first GLP-1 receptor agonist specifically approved for weight loss in patients without a history of type 2 diabetes, with the brand name Saxenda®. It is FDA-approved in adult patients with a body mass index greater than 30 kg/m^2 alone or greater than 27 kg/m^2 in the presence of at least one weight-related comorbidity, such as hypertension, diabetes, or dyslipidemia. The dose for this indication is 3.0 mg/day, which is higher than the maximum dose of 1.8 mg/day approved for type 2 diabetes. It comes in a different pen device, with a 5-week dose titration schedule [48]. In a double-blind, placebo-controlled trial comparing the weight loss drug orlistat, placebo, and different doses of liraglutide, participants on liraglutide lost significantly

Table 1. General weight loss observed with GLP-1 receptor agonists based upon package inserts (kg).

Dulaglutide [35]		Albiglutide [30]	Liraglutide [22]		Exenatide QW [26]	Exenatide BID [17]	
0.75 mg dose	1.5 mg dose		1.2 mg dose	1.8 mg dose		5 mg BID	10 mg BID
(+0.2)–(–2.7)	(–0.9)–(–3.1)	(–0.4)–(–1.1)	(+0.3)–(–2.6)	(–0.2)–(–2.8)	–2.3 kg	(–1.1)–(–2.7)	(–1.6)–(–2.9)

Weight loss ranges based upon trials in the package inserts. Background medications differed in the trials, potentially contributing to the range in weight gain/weight loss.

Table 2. Exenatide weekly studies—CV outcomes.

Study	N	Background OAD	Comparator	A1C reduction with exenatide (%)	Change in body weight (kg)	Change in SBP (mmHg)	Change in DBP (mmHg)	Change in Tchol (mg/dL)	Change in LDL (mg/dL)	Change in TG (%)
DURATION-1 [6,42]	295	SU	ExBID	–1.9	–3.7	–4.7	–1.7	–11.97	–5.01	–15
DURATION-2 [42,46]	491	MET	Sitagliptin, pioglitazone	–1.5	–2.3	–4	None	–0.386	–0.77	–5
DURATION-3 [29,42]	456	MET±SU	Insulin glargine	–1.01	–2.6	–3	–1	–4.63	–1.93	–4
DURATION-4 [58]	820	None	MET, pioglitazone, sitagliptin	–1.53	–2.0	–1.3	0	None	None	None
DURATION-5 [42,55]	252	MET+TZD	ExBID	–1.6	–2.3	–2.9	0.2	NA	NA	NA
DURATION-6 [28,42]	911	MET, SU, TZD	Liraglutide	–1.28	–2.68	–2.48	–0.49	–2.31	–1.93	NA

N, patients enrolled in the study (all studies done with exenatide 2 mg weekly); SU, sulfonylurea; ExBID, exenatide twice daily; MET, metformin; TZD, thiazolinedione; OAD, oral antidiabetic drug. Adapted from Mundil et al. and Duration trials 1–6.

more weight. The group taking 3.0 mg/day of liraglutide lost the most weight of 7.2 kg after 20 weeks compared to 4.1 kg on orlistat and 2.8 kg on placebo. Pre-diabetes was also reduced by 84–96% in the high dose liraglutide group [49].

Blood pressure and lipids

The GLP-1 receptor agonists have demonstrated positive effects on blood pressure and lipid parameters. most of the data are on liraglutide and exenatide since they have been available the longest. In clinical trials, liraglutide consistently reduced systolic blood pressure (SBP) from 2.5 to 5.5 mmHg from baseline utilizing the 1.2 and 1.8 mg daily doses. Diastolic blood pressure (DBP) was reduced from 0 to 1.7 mmHg [7,50–54]. Exenatide had similar blood pressure reductions ranging from 2.9 to 4.7 mmHg for systolic blood pressure and 0 to 1.9 mmHg for diastolic blood pressure in the Duration trials [6,29,55,56]. In the Harmony-3 trial with albiglutide, an SBP and DBP reduction of 1.5/1.0 mmHg at week 104 was observed [57].

Specific effects on weight, blood pressure, and lipids of exenatide weekly and liraglutide obtained from clinical trials are listed in Tables 2 and 3. Effects of albiglutide on weight are presented in Table 4.

Beta-cell function

At time of a formal type 2 diabetes diagnosis, approximately 50% of beta-cell function is lost [62]. Many of the medications used to treat type 2 diabetes fail to maintain glycemic control for a long term due to disease progression and decline in beta-cell function [63]. Because the pancreatic beta cells are responsible for insulin secretion, there is great interest in protecting beta-cell function and potentially reversing the clinical course of diabetes. The GLP-1 receptor agonists cause glucose-dependent insulin response and, therefore, protect beta cells against cytokine-induced apoptosis [45]. Clinical trials have demonstrated improvements in surrogate markers of beta-cell function with use of GLP-1 receptor agonists [64]. Specifically, dulaglutide and liraglutide increased HOMA2-B, a marker of beta-cell function. Rodent models have demonstrated increases in beta-cell mass as well, via cellular regeneration and inhibition of apoptosis [65]. GLP-1

Table 3.   Liraglutide (Victoza®) studies—CV outcomes.

Study	N	Background OAD	Comparator	A1C reduction with liraglutide (%)	Change in body weight (kg)	Change in SBP (mmHg)	Change in DBP (mmHg)	Change in pulse rate (bpm)	Change in Tchol (mg/dL)	Change in LDL (mg/dL)	Change in TG (mg/dL)
LEAD-1 [42,50]	1041	SU	TZD or placebo	−1.1	−0.2*	−2.8	−1.4	+2 to +4*	NA	NA	NA
LEAD-2 [42,51]	1091	MET	SU or placebo	−1.0	−2.8*	−2.3*	None	+2 to +3*	NA	NA	NA
LEAD-3 [42,52]	746	None	SU	−1.14	−2.5*	−3.6*	None	+1.6	NA	NA	NA
LEAD-4 [42,53]	533	MET+TZD	Placebo	−1.5	−2.0*	−5.6*	−1.9	+3*	−7.72	−8.88	−28.31
LEAD-5 [42,54]	581	MET+SU	Insulin glargine or placebo	−1.33	−1.8*	−4.0*	None	+2.62*	NA	NA	NA
LEAD-6 [7,42]	464	MET+SU	Exenatide	−1.12	−3.2	−2.5	−1.05	+3.28*	−7.72	−16.98	−36.28

Reference: LEAD 1–LEAD 6, Mundil et al.
*Statistically significant compared with comparator drug.
SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione.

Table 4.   Abliglutide (Tanzeum®) clinical trials: changes in weight and hemoglobin A1C [81].

Study	N	Background OAD	Comparator	A1C reduction with abliglutide	Change in body weight (kg) over study period
HARMONY I [60]	1041	TZD	Placebo	Albiglutide 30 mg: −0.81%	+0.3
HARMONY 2 [32]	1091	None	Placebo	Albiglutide 30 mg: −0.84% Albiglutide 50 mg: −1.04%	−0.4
HARMONY 3 [57]	746	MET	Placebo, SU, Sitagliptin	Albiglutide 30–50 mg: −0.63%	−1.21
HARMONY 4 [33]	533	MET±SU	Insulin glargine	Albiglutide 30–50 mg: −0.67%	−1.1
HARMONY 5 [59]	581	MET±SU	Placebo, pioglitazone	Albiglutide 30–50 mg: −0.55%	−0.4
HARMONY 6 [61]	464	Insulin glargine	Insulin glargine+insulin lispro	Albiglutide 30–50 mg: −0.82%	−0.73
HARMONY 7 [34]		Met or SU or TZD	Liraglutide	Albiglutide 50 mg: −0.78%	−0.64

OAD, oral antidiabetic drug; TZD, thiazolinedione; MET, metformin; SU, sulfonylurea.

receptor agonists also improve insulin resistance and glucose homeostasis, which is thought to provide an overall benefit to the beta cells [66].

Safety issues

Common adverse effects

Clinical trials with GLP-1 receptor agonists have reported the most common adverse effect as gastrointestinal in nature, which include diarrhea, nausea, and vomiting [47,67]. Over time, these are often self-limiting for many patients. Less

than 5% discontinued these agents in clinical trials due to gastrointestinal effects, although higher rates of discontinuation (5–10%) are seen in clinical practice. Adverse effects are more common with higher doses, and will typically improve over time. Slow dose-titration helps to reduce these effects [63,64].

The GLP-1 receptor agonist, taspoglutide, was developed to have a longer duration of action than liraglutide and was studied in the T-EMERGE clinical trials in over 6000 patients. T-EMERGE-2 was a long-term study to compare the efficacy and safety of taspoglutide once weekly with exenatide twice daily in patients with type 2 diabetes. Participants received taspoglutide 10 mg weekly (n=399) or taspoglutide 20 mg

Table 5.   Comparison of adverse effects between GLP-1 receptor agonists.

Adverse reactions	Albiglutide [30]		Dulaglutide [35]			Liraglutide [22]	Exenatide QW [26]	Exenatide BID [17]	
N	Albiglutide N=923, %	Placebo N=468, %	Dulaglutide 0.75 mg N=834, %	Dulaglutide 1.5 mg N=836, %	Placebo N=568, %	Liraglutide N=497, %	Exenatide N=248, %	Exenatide N=963, %	Placebo N=483, %
Diarrhea	13.1	10.5	8.9	12.6	6.7	17.1	10.9	13	6
Nausea	11.1	9.6	12.4	21.1	5.3	28.4	11.3	44	18
Vomiting	4.2	2.6	6.0	12.7	2.3	10.9	NA	13	4
Injection-site reaction or nodules	10.5	2.1	0.5	0.5	0	NA	10.5	NA	NA

weekly (n=398) or exenatide 10 μg twice daily (n=392). Both exenatide and taspoglutide significantly reduced hemoglobin A1C, fasting plasma glucose, and body weight without severe hypoglycemia. However, the overall safety profile of taspoglutide 20 mg weekly was worse than exenatide 10 μg daily, which included more gastrointestinal effects (21.6 vs 10.1%), hypersensitivity (4.1 vs 0.8%), and injection-site reactions (10.9 vs 0.8%). The taspoglutide 10 mg weekly had less adverse effects than the 20 mg weekly dose, but was still worse than exenatide. Almost twice as many patients in the taspoglutide arm withdrew from the study. It has been suggested that the greater nausea and vomiting with taspoglutide may reflect some of the pharmacokinetic differences, and usually these effects were worse on the day of injection. Due to the high rates of adverse effects and high discontinuation rate from the study, trials were halted in September 2010, and this drug is not expected to come to market [68].

Table 5 compares common adverse effects between the marketed GLP-1 receptor agonists. In clinical trials, there were few serious adverse effects such as major episodes of hypoglycemia, and when hypoglycemia did occur, it was typically associated with concomitant insulin or insulin secretagogues [47]. Thus, it is recommended to decrease the dose of these concomitant agents when adding a GLP-1 agonist [64].

Cardiovascular safety

In 2008, the FDA recommended that all drugs investigated for diabetes should be evaluated for cardiovascular effects since patients with diabetes have a two to four times greater risk of developing cardiovascular disease compared with patients without diabetes. Treatment for type 2 diabetes is usually life-long, and none of the medications utilized to treat diabetes have strong evidence to support mitigating this risk. Phase two and three trials are now required to demonstrate that they do not increase cardiovascular risk in comparison to existing

therapies, especially when used in patients with advanced age or declining renal function [69].

Overall, GLP-1 receptor agonists have demonstrated positive cardiovascular outcomes with slight improvements in blood pressure and lipid parameters and modest improvements in weight. However, increases in hospitalizations due to heart failure have been observed with oral incretin therapy, DPP-4 inhibitors, and specifically saxagliptin in the SAVOR trials. Still, studies with other DPP-4 inhibitors and GLP-1 receptor agonists have thus far not demonstrated this increase in heart failure exacerbations or hospitalizations [64]. A meta-analysis of 33 trials consisting of exenatide twice daily, exenatide weekly, liraglutide, taspoglutide, and albiglutide showed no increase in major cardiovascular events, including myocardial infarctions, strokes, and all-cause mortality, when compared to other agents or placebo [70]. In an analysis of 15 studies of liraglutide, major adverse cardiovascular events were <1% and considered equivalent to that of placebo or comparator arms. The upper 95% confidence interval was <1.8, and considered within cardiovascular safety limits as posed by the FDA [71].

Smaller studies have suggested that insulin-induced hypoglycemia is associated with prolongation of the QT interval. GLP-1 receptor agonists have low risk of hypoglycemia when administered alone, although the risk rises when combined with other drugs that increase hypoglycemic risk. Thus far, studies and post-marketing reports with exenatide and liraglutide have not demonstrated any prolongation of the QT interval.

Exenatide and liraglutide have been associated with increases in heart rate (1–2 beats/minute), although an integrated analysis of 12 randomized, controlled trials with exenatide showed only an average 0.5 beats/minute increase. It is unknown if this has any clinical significance on cardiovascular outcomes [72]. However, since these agents have not been on the market for an extended duration, there is a lack of long-term safety data on cardiovascular mortality and other long-term cardiovascular parameters [42].

The LEADER trial is underway to examine the long-term effects of liraglutide 1.8 mg on cardiovascular death, nonfatal myocardial infarction, and stroke as a primary outcome in 6000 patients. It began recruitment in 2010. Another study, the EXSCEL trial, has been testing cardiovascular safety of exenatide 2 mg weekly in 9500 patients with type 2 diabetes over a period of 5.5 years. Other trials assessing cardiovascular outcomes are also underway with dulaglutide and lixisenatide. When the results from these trials are available, there will be more definitive answers on the relationship between GLP-1 receptor agonists and cardiovascular safety [73].

Acute pancreatitis

Cases of acute pancreatitis have been reported in animals and humans treated with GLP-1 receptor agonists as well as DPP-4 inhibitors. However, these animal studies have been inconsistent, with some showing damage to the pancreas, some being neutral, and some showing potential improvement. When exenatide twice daily first became available, there was reporting of exenatide-induced pancreatitis. This led the FDA to release a warning that post-marketing studies of exenatide may suggest a link between treatment and acute pancreatitis, and that healthcare professionals should monitor for signs of pancreatitis in patients using these agents [42].

Retrospective observational studies have found virtually no increase in cases of pancreatitis with incretin-based therapy, although there is a lack of prospective trials to say for certain that there is no correlation [64]. To date, there have been no reported cases of clinically identifiable chronic pancreatitis or pancreatic cancer proven to be caused from incretin-based therapies. Some histological samples taken from organs of those with type 2 diabetes and who took incretins demonstrated pancreatic abnormalities, but it is not known if other confounders may have caused this, as patients with diabetes often exhibit a baseline increased risk of pancreatitis when compared to patients without diabetes. Since these agents were approved only in 2005, it may be too early to know for sure if there is any link [64]. In clinical trials, rates of pancreatitis have been low. For example, in the T-EMERGE-2 trial with exenatide and taspoglutide, there was only one case of pancreatitis, and it was unknown whether it was related to treatment or other ancillary causes [68]. Treatment guidelines recommend to use GLP-1 receptor agonists cautiously in patients with a history of pancreatitis and to discontinue if acute pancreatitis develops during use [67].

Medullary thyroid carcinoma

Exposure to long-acting GLP-1 receptor agonists has demonstrated an increase in thyroid C-cell hyperplasia, adenomas, and medullary thyroid carcinomas in mice, although not in humans. Rodent C-cells have considerably more GLP-1 receptors than humans, which may explain the increase in some animal studies. Mice also develop thyroid C-cell

carcinomas at much higher rates than humans, and increases have been observed even in mice treated with placebo. In general, medullary thyroid carcinoma in humans is very rare [64]. Furthermore, in clinical trials and post-marketing surveillance, GLP-1 receptor agonist use has not demonstrated any cases of medullary thyroid carcinomas [64]. Nonetheless, all GLP-1 receptor agonists, with the exception of exenatide twice daily, are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple neoplasia syndrome type 2 [22,26,30,35]. At this time, the FDA does not require specific monitoring for medullary thyroid carcinoma [67].

Antibody formation

GLP-1 receptor agonists are therapeutic peptides and, therefore, there is concern that antidrug antibodies could develop leading to decreased efficacy or increased hypersensitivity reactions over time. Increased hypersensitivity reactions occurred with tapsoglutide, which was one of the reasons for discontinuing clinical trials and for the agent not coming to market. Taspoglutide has 93% homology with endogenous GLP-1 and a higher than expected incidence of skin reactions, gastrointestinal symptoms, and antidrug antibodies [42]. Antibody levels have been measured in clinical trials, with significant variation between the various GLP-1 receptor agonists, which is thought to be due to differences in immunogenicity of the formulations. newer formulations, including albiglutide and dulaglutide, have less risk of antibody formation compared to exenatide and liraglutide [63]. Exenatide produces the most antibodies out of the marketed GLP-1 receptor agonists, possibly due to the lower sequence identity of exenatide with native GLP-1 [63]. Among the two exenatide formulations, exenatide weekly produces more antibodies than exenatide twice daily [73]. Data from 17 clinical trials with exenatide reported that 36.7% of exenatide twice daily patients were antibody positive, 31.7% with low titers and 5.0% with higher titers. Antibody incidence declined to 16.9% after 3 years. With weekly exenatide, 56.8% of patients were antibody positive, including 45.0% with low titers and 11.8% with high titers, which declined to 45.4% positive at 52 weeks. Higher rates of injection-site reactions were observed in patients with antibody-positive titers, but other adverse effects were not statistically different. Those with high antibody titers overall had a smaller improvement in hemoglobin A1C values; however, there was no correlation found in hemoglobin A1C values between patients with negative titers versus those with low titers [74].

Renal effects

There is some evidence that GLP-1 receptor agonists have a protective role in diabetic nephropathy [75]. However, there are also associations of GLP-1 receptor agonists with acute kidney injury [16]. Exenatide is eliminated by renal mechanisms, and

Table 6.   Renal and hepatic adjustments of GLP-1 agonists.

	Dose adjustment for renal impairment	Dose adjustment for hepatic impairment
Exenatide twice daily [17]	Not appropriate for patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease. Caution should be applied when initiating or escalating doses from 5 to 10 µg in patients with moderate renal impairment (CrCL 30–50 mL/min).	Exenatide undergoes renal elimination, thus hepatic impairment is not expected to affect blood concentrations. Dose adjustment is not indicated.
Liraglutide [22]	Few post-marketing reports of acute renal failure with liraglutide exist in patients with pre-existing kidney disease. Utilize with caution in patients with chronic kidney disease. Dose adjustment is not recommended.	Dose adjustment is not necessary.
Exenatide once weekly [26]	Not recommended for use in patients with end-stage renal disease or severe renal impairment (CrCL <30 mL/min). Exercise caution in patients with moderate renal impairment (CrCL 30–50 mL/min). Dose adjustment is not necessary.	Exenatide undergoes renal elimination, thus hepatic impairment is not expected to affect blood concentrations. Dose adjustment is not indicated.
Dulaglutide [35]	Dose adjustment is not necessary. Exercise caution when initiating or escalating doses in patients with renal impairment.	Dose adjustment is not necessary.
Abliglutide [30]	Dose adjustment is not necessary. Exercise caution when initiating or escalating doses in patients with renal impairment.	Dose adjustment is not necessary.

CrCL, creatinine clearance.

it is not recommended for use in patients with severe renal impairment or end-stage renal disease [17]. In 2009, the FDA approved revisions to the drug label for exenatide to include information on post-marketing reports of altered kidney function [16]. Between 2005 and 2008, the FDA received 78 reports of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency) in patients using exenatide twice daily, 71 of which required hospitalization. During this time, more than six million prescriptions were dispensed for exenatide, emphasizing that this was a small number overall and that many patients had pre-existing kidney disease or risk factors for altered kidney function, such as cardiac insufficiency, hypertension, and urinary tract infection, or were taking concomitant medications, such as nonsteroid anti-inflammatories drugs, that increase the risk of renal insufficiency [76]. Main adverse effects of GLP-1 receptor agonists include nausea and vomiting, which may result in decreased fluid intake and fluid loss, which can potentially lead to acute renal failure. Liraglutide is not eliminated renally [22], and mild renal impairment has not demonstrated a significant effect on its efficacy or safety, although there have been case reports of acute kidney injury with use of liraglutide in patients with moderate to severe renal impairment [75]. Albiglutide once weekly was studied in a phase 3 trial compared to sitagliptin in

patients with renal impairment and was found to be superior with similar tolerability. Of note, albiglutide does not require renal elimination or any dose adjustments for renal impairment [77]. Dulaglutide also does not require any renal dose adjustments. However, both dulaglutide and albiglutide have been associated with a higher incidence of gastrointestinal reactions as renal function declined. Per the package inserts of both agents, it is recommended to monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions [30,35]. Table 6 shows the various renal and hepatic adjustments necessary for GLP-1 receptor agonists and outlines considerations that need to be taken with individual agents.

Place in therapy

Metformin is considered first line in the treatment of type 2 diabetes according to guidelines from the American Diabetes Association, European Association for the Study of Diabetes, and American Association of Clinical Endocrinologists [2,3,67]. All guidelines recommend GLP-1 receptor agonists as potential add-on therapy to metformin for patients with uncontrolled type 2 diabetes. They also may be considered as monotherapy for patients intolerant to metformin. Current

guidelines advocate a personalized approach with a focus on mechanism of action, efficacy, and safety of the agents, as well as other patient-specific factors, such as cost, adherence, patient preferences, and likelihood of reaching goal hemoglobin A1C [2,67].

GLP-1 receptor agonists hold many advantages over other diabetes treatments. They are attractive as add-on therapy because of their ability to increase insulin secretion and inhibit glucagon release, but only when glucose levels are elevated [63]. This is different from sulfonylureas and glitinides, which cause insulin secretion regardless of glucose levels and explains why they are associated with higher rates of hypoglycemia. Insulin therapy, although highly effective in reducing hemoglobin A1C, carries the disadvantage of causing hypoglycemia. Both thiazolidinediones and insulin are associated with weight gain [78] compared to the GLP-1 receptor agonists that overall result in weight loss.

GLP-1 receptor agonists have been studied in combination with several of the oral antidiabetic agents. Many diabetes medications can be combined together successfully to work synergistically on the multiple organ defects involved in type 2 diabetes. However, current guidelines do not recommend combining GLP-1 receptor agonists with DPP-4 inhibitors [3,67], likely due to the duplication in mechanism of action and lack of clinical outcomes and experience with this combination. Current guidelines also do not make a recommendation on the combination with sodium-glucose cotransporter-2 inhibitors due to the lack of clinical trial data with this combination.

GLP-1 receptor agonists have also been studied with insulin and are an option for add-on therapy to basal insulin in place of prandial insulin. They reduce postprandial glucose, and, when combined with insulin, may allow for reduced insulin doses [3]. This may translate into multiple benefits including less weight gain, hypoglycemia, and insulin resistance. Exenatide, albiglutide, and liraglutide all have FDA-approved indications for concomitant use with basal insulin. At the time of this writing, dulaglutide has not yet been approved in combination with insulin [31], and none of the GLP-1 recent agonists are marketed for use with basal and bolus insulin regimens. There is limited information about the clinical outcomes with this combination. Theoretically, it may also increase injection burden on the patient.

The first insulin and GLP-1 receptor agonist combination pen was recently approved by the European Union, which contains long-acting insulin degludec and liraglutide. This pen contains a fixed ratio of insulin degludec 100 units and liraglutide 1.8 mg per mL. Doses can be adjusted by 1 unit of insulin degludec and 0.036 mg of liraglutide with the maximum dose at one time of 50 units of insulin degludec and 1.8 mg of liraglutide. One of the drawbacks to this fixed-dose combination is the lack of flexibility in dosing, but this does allow for less daily injections. This combination was studied in the DUAL clinical trials (DUAL1 and DUAL II) and demonstrated

superior glycemic control over insulin degludec or liraglutide alone with benefits on weight loss when compared to insulin degludec [79,80].

Long-term durability of GLP-1 receptor agonists is not known. Most studies ranged from 12 to 36 weeks. In a meta-analysis, patients on basal insulin plus GLP-1 receptor agonists, as compared to basal insulin with other diabetes drugs, were 92% more likely to achieve target hemoglobin A1C less than 7% [78]. Unfortunately, these agents tend to have a higher cost than other approved agents, especially when compared to metformin, sulfonylureas, and thiazolideinediones, which all have generics available.

Comparison to DPP4 inhibitors

The other class of drugs that affects incretins is DPP4 inhibitors, which work by suppressing the enzyme DPP4 that normally degrades endogenous GLP-1, therefore increasing the concentration of biologically active GLP-1. However, GLP1 receptor agonists have an advantage over DPP4 inhibitors in that they can reach supratherapeutic levels of GLP-1, beyond that of which is capable biologically. GLP-1 receptor agonists appear to be superior in reducing hemoglobin A1C concentrations [21] and have the added benefits of slowing the rate of gastric emptying and causing a sense of satiety leading to reduced food intake and moderate weight loss. In contrast, the DPP-4 inhibitors are considered weight neutral [64]. A benefit of DPP-4 inhibitors is that they are available for oral administration, while all GLP-1 receptor agonists are only injectable formulations. However, the weekly regimens of GLP-1 agonists may potentially improve patient adherence.

Patient-specific drug selection

With five agents to choose from in the United States and six to choose from in Europe, there are several factors to take into consideration when selecting a specific GLP-1 receptor agonist to use in a patient. None of the agents are available generically, and therefore all have a relatively high cost. Agent choice may be dependent on formulary considerations and what a patient's individual insurance plan will cover. Important differences between agents include dosing frequency and whether they have stronger effects on postprandial or fasting blood glucose. In general, the longer-acting formulations, including exenatide weekly, dulaglutide, and albiglutide, and even liraglutide, have demonstrated greater effects on fasting blood glucose, while the shorter-acting agents, such as exenatide twice daily and lixisenatide, have a greater impact on postprandial glucose lowering. Therefore, depending on when the individual patient is experiencing glucose elevations, may be a contributing factor in choosing one of these formulations over the other. Other considerations are adverse effects. For example, albiglutide demonstrated less of an effect on hemoglobin A1C reduction in clinical trials compared to liraglutide, but also had less incidence of adverse effects [34]. Renal function is an important

consideration, and while all should be monitored closely in patients with renal impairment, exenatide should not be used in patients with a creatinine clearance less than 30 mL/min.

An important consideration is patient adherence to therapy. Once-weekly injections reduce injection burden, although may be more difficult for patients to get into a habit of taking. Another consideration is administration and ease of agent use. Albiglutide and exenatide weekly require reconstitution by the patient before use. This extra step may be difficult for some patients, including those with visual impairment, dexterity issues, or health literacy concerns. It is especially important that these patients are educated on these additional steps. The combination of liraglutide with insulin degludec may be an attractive option for some patients, although it provides less flexibility with dosing and is currently only available in Europe [78]. Regardless of which drug is ultimately selected, the dose should be gradually titrated according to the recommended product labeling to minimize toxicity, and patients should be monitored for efficacy and tolerability.

Monitoring

Because many of the GLP-1 receptor agonists are affected by renal impairment, monitoring serum creatinine and creatinine clearance is especially important [17,26]. Even with dulaglutide and albiglutide, which do not have dose adjustments for renal impairment, adverse effects may be worse in patients with impaired renal function, and therefore should still be monitored [30,35]. In all cases of diabetes, hypoglycemia reactions should be monitored, especially if the patient is using a GLP-1 receptor agonist in conjunction with insulin or insulin secretagogues. While these agents carry black-box warnings for medullary thyroid carcinoma, routine monitoring for this condition, such as obtaining calcitonin levels, is generally not recommended [67]. Although pancreatitis appears to be rare, educating the patient about symptoms of pancreatitis, such

as extreme abdominal pain, is important. As with all patients with diabetes, hemoglobin A1C should be monitored every 3–6 months depending on glycemic control [2,67]. Self-monitoring of blood glucose (SMBG) is recommended and may help guide dosing adjustments. For example, if a patient is not meeting SMBG goals on liraglutide 1.2 mg daily, then there is an option to increase to 1.8 mg daily. However, there is not a consensus on the number of times a patient taking a GLP-1 receptor agonist should test SMBG. Other monitoring should include close follow-up with a healthcare professional to assess gastrointestinal side effects, such as nausea, vomiting, and diarrhea. These agents should be avoided in patients with gastroporesis or inflammatory bowel disease due to their effects of slowed gastric emptying and potential exacerbation of disease [16,26].

Conclusion

GLP-1 receptor agonists are effective agents for the treatment of type 2 diabetes, offering many advantages over other agents, including weight loss, potential beta-cell protection, and low risks of hypoglycemia. They also have positive benefits on cardiovascular parameters, including reductions in blood pressure, lipids, and weight, although the clinical relevance of this remains to be determined. Additionally, because GLP-1 receptor agonists are available in a variety of forms, including twice-daily injections, once-daily injections, and once-weekly injections, patient satisfaction with these agents may be improved—as the patient is able to utilize the agent that bests fits his or her lifestyle. Although long-term safety data is unavailable due to the short duration of time that these agents have been on the market, future studies will provide guidance to practitioners on the appropriate choice of agents to mitigate risk, including cardiovascular risk. Overall, GLP-1 receptor agonists are effective and innovative agents for patients with type 2 diabetes and other chronic conditions, who are either uncontrolled or intolerant to first-line metformin therapy.

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