review article

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REVIEW

Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists

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Currently, six glucagon-like peptide-1 receptor agonists (GLP-1RAs) are approved for treating type 2 diabetes. These fall into two classes based on their receptor activation: short-acting exenatide twice daily and lixisenatide once daily; and longer-acting liraglutide once daily, exenatide once weekly, albiglutide once weekly and dulaglutide once weekly. The phase III trial of a seventh GLP-1RA, taspoglutide once weekly, was stopped because of unacceptable adverse events (AEs). Nine phase III head-to-head trials and one large phase II study have compared the efficacy and safety of these seven GLP-1RAs. All trials were associated with notable reductions in glycated haemoglobin (HbA1c) levels, although liraglutide led to greater decreases than exenatide formulations and albiglutide, and HbA1c reductions did not differ between liraglutide and dulaglutide. As the short-acting GLP-1RAs delay gastric emptying, they have greater effects on postprandial glucose levels than the longer-acting agents, whereas the longer-acting compounds reduced plasma glucose throughout the 24-h period studied. Liraglutide was associated with weight reductions similar to those with exenatide twice daily but greater than those with exenatide once weekly, albiglutide and dulaglutide. The most frequently observed AEs with GLP-1RAs were gastrointestinal disorders, particularly nausea, vomiting and diarrhoea. Nauseaoccurred less frequently, however, with exenatide once weekly and albiglutide than exenatide twice daily and liraglutide. Both exenatide formulations and albiglutide may be associated with higher incidences of injection-site reactions than liraglutide and dulaglutide. GLP-1RA use in clinical practice should be customized for individual patients, based on clinical profile and patient preference. Ongoing assessments of novel GLP-1RAs and delivery methods may further expand future treatment options.

Keywords: albiglutide, dulaglutide, exenatide, GLP-1 receptor agonist, liraglutide, lixisenatide, taspoglutide, type 2 diabetes

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Introduction

The early and intensive treatment of people with type 2 diabetes (T2D) is of key importance for reducing the risk of late diabetic complications, such as microvascular disease [1]. T2D is linked to obesity [2], and the cornerstone of treatment is lifestyle changes to promote weight loss and increase exercise [3]; however, because of the progressive nature of T2D, pharmacological therapy to address hyperglycaemia becomes necessary in almost all patients. Pharmacological treatment is, unfortunately, often associated with side effects such as weight gain (e.g. sulphonylureas, insulin and thiazolidinediones) [4,5], hypoglycaemia (e.g. sulphonylureas and insulin) [6,7], gastrointestinal (GI) discomfort [e.g. metformin and glucagon-like peptide-1 receptor agonists (GLP-1RAs)] and genital infections [sodium-glucose co-transporter 2 (SGLT2) inhibitors] [8–10]. Notwithstanding the GI discomfort with GLP-1RAs, their introduction over the last decade has greatly improved treatment of T2D [11–14].

Human GLP-1 is a member of the incretin family of glucoregulatory hormones, and is secreted in response to food ingestion [15,16]. Glucagon-like peptide-1 has multiple effects that are desirable in the treatment of T2D, including: glucose-dependent increased insulin secretion; glucose-dependent decreased glucagon secretion; delayed gastric emptying; increased satiety; and, as shown in some animal studies, protection of β-cell mass [17,18].

Unfortunately, although intravenously infused GLP-1 can normalize plasma glucose concentrations in people with T2D [19,20], it has an extremely short half-life (1–2 min) [16] that limits its therapeutic value [21]. Multiple GLP-1RAs have been developed to recapitulate the physiological effects of GLP-1 but with an extended duration of action (achieved by various changes to the molecular structure) compared with the native peptide [22].The present review examines the available evidence from published head-to-head clinical trials with GLP-1RAs, and contrasts the relative clinical benefits of the short- and longer-acting agents.

Characteristics of GLP-1RAs

Seven GLP-1RAs are included in the present review, all of which have been studied in phase III clinical trials. The GLP-1RAs are: exenatide twice daily (Byetta®, AstraZeneca; approved in Europe in November 2006 and 28 May 2005 in USA [23,24]); liraglutide (Victoza®, Novo Nordisk; approved in Europe in June 2009 and 25 January 2010 in USA [25,26]); exenatide once weekly (Bydureon®, AstraZeneca; approved in Europe in

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June 2011 and 26 January 2012 in USA [27,28]); lixisenatide (Lyxumia®, Sanofi; approved in Europe in February in 2013 [29] but not in the USA); albiglutide (Eperzan® and Tanzeum®, GlaxoSmithKline; approved in March 2014 in Europe and April 2014 in USA [30,31]); dulaglutide (Trulicity™, Lilly; approved in Europe in November 2014 and September 2014 in USA [32,33]); and taspoglutide (Ipsen/Roche). These have all now been approved for use in T2D, with the exception of taspoglutide, the development of which was halted because of serious hypersensitivity reactions and GI adverse events (AEs) during clinical trials; however, the available data for this compound are included in the present review to give a full picture of the GLP-1RA family.

As a drug class, the GLP-1RAs have proven efficacy for lowering glycated haemoglobin (HbA1c) and decreasing weight in T2D, with a reduced risk of hypoglycaemia compared with insulin or sulphonylureas [34]. These characteristics underlie the inclusion of GLP-1RAs in various clinical practice guidelines. Their use as dual therapy with metformin after first-line metformin and as triple therapy (in combination with metformin and a sulphonylurea/thiazolidinedione/insulin) is part of the European Association for the Study of Diabetes/American Diabetes Association recommendations [34]. GLP-1RAs are recommended as monotherapy, dual therapy and triple therapy by the American Association of Clinical Endocrinologists/American College of Endocrinology guidelines [35]. Nonetheless, they differ substantially in their molecular structure and degree of homology to endogenous GLP-1, both in their chemical and physiological properties and in their durations of action (Table 1).

Several GLP-1RAs (exenatide twice daily, exenatide once weekly and lixisenatide) are based on the exendin-4 molecule, a peptide with 53% identity to native GLP-1 [36,42,43], while others, such as liraglutide, albiglutide, dulaglutide and taspoglutide are classified as GLP-1RA analogues with 97, 95, 90 and 93% identity, respectively, to native GLP-1 [38–40]. The GLP-1RAs are, in addition, commonly considered to fall into two different classes based on their duration of receptor activation. The short-acting compounds, delivering short-lived receptor activation, comprise exenatide twice daily and lixisenatide once daily. The long-acting compounds, which activate the GLP-1 receptor continuously at their recommended dose, comprise liraglutide once daily, and the once-weekly formulations of exenatide, albiglutide, dulaglutide and taspoglutide (Table 1). These different durations of action largely explain variations among GLP-1RAs in their impact on fasting plasma glucose (FPG), 24-h glucose profile and postprandial plasma glucose (PPG) levels [60,61]. Delayed gastric emptying, for example, is more strongly associated with short-acting than longer-acting GLP-1RAs (Figure 1), and this may underlie the greater effects on PPG observed with short-acting GLP-1RAs. Meanwhile, the greater half-lives of the longer-acting compounds allow enhanced effects on the whole 24-h glucose level, including FPG. Longer-acting GLP-1RAs do not significantly affect gastric motility. Instead, they exert more of their effect via the pancreas, increasing insulin secretion and inhibiting glucagon secretion via paracrine release of somatostatin (Figure 1) [22].

Not only do GLP-1RAs differ from each other in terms of their duration of action [39,46–51], they also show varying levels of affinity for the GLP-1 receptor [62]. This difference between GLP-1RAs is also evident in their varying efficacy with regard to HbA1c reduction and weight loss, and differing tolerability profiles and potential for immunogenicity [22,63–65]. It is important to understand these specific characteristics to appropriately tailor the choice of GLP-1RA to the individual patient. Head-to-head clinical trials are the best way to elucidate variations in efficacy and tolerability, and a number of such studies have been conducted with GLP-1RAs in T2D.

Head-to-head Comparison Trials

To date, the results from nine phase III randomized trials that directly compare different pairs of GLP-1RAs have been published [12–14,40,54–56,66,67]. An overview of the designs of these studies is provided in Table 2. One large phase II study, comparing liraglutide and lixisenatide pharmacodynamics, is also included [61].

Of the GLP1-RAs in the head-to-head trials, exenatide twice daily and liraglutide were the most common comparators (Table 2). The majority of the phase III studies included in the present review were of ~6 months' duration, although several also had extension phases to give trial durations up to 12 months (Table 2). All of the phase III trials examined changes in HbA1c as the primary endpoint; the phase II study by Kapitza et al. [61], however, used changes in PPG exposure as the primary endpoint.

In general, baseline characteristics were similar across trial populations and between treatment groups within individual trials (Table 3). The mean age of participants ranged from 55 to 61 years across the studies, with mean duration of diabetes ranging from 6 to 9 years. Mean baseline HbA1c levels were in the range of 8.0 (64 mmol/mol) to 8.7% (72 mmol/mol) across the studies, except for the phase II study (in which HbA1c levels were lower) [61]. Glucose concentrations in the range of 9.1–9.9 mmol/l were determined in plasma and serum samples, and mean baseline weight was consistently in the range 91–102 kg, except in an Asian study, in which mean weight was lower [56] (Table 3). Differences in key study outcomes are discussed in the following sections.

Glycaemic Measurements

In all of the head-to-head trials, the GLP-1RAs studied led to notable reductions in HbA1c.

These reductions ranged between 0.3 (3 mmol/mol) and 1.9% (21 mmol/mol). Although data are not comparable across studies because of differences in study design and patient cohorts, there were some important differences between treatment arms in the magnitude of HbA1c reductions (Figure 2). In particular, in the DURATION-1, DURATION-5 studies and the study by Ji et al. [54–56], exenatide once weekly produced both more consistent and greater reductions in HbA1c levels than did exenatide twice daily ($p \leq 0.0023$). In the GetGoal-X study [12], meanwhile, exenatide twice daily showed a numerically greater HbA1c reduction than lixisenatide. Liraglutide, in

Table 1. Comparative characteristics of the glucagon-like peptide-1 receptor agonists.

	Exenatide twice daily	Exenatide once weekly	Liraglutide once daily	Lixisenatide once daily	Albiglutide once weekly	Dulaglutide once weekly	Taspoglutide once weekly
Percentage amino acid sequence similarity to native GLP-1	53% [36]	53% [36]	97% [37]	≈50%*	95% [38]	90% [39]	93% [40]
Properties of the drug	Resistant to DPP-4 cleavage, largely due to the substitution of alanine in position 2 by glycine [41]	Encapsulated in biodegradable polymer microspheres [42]	C-16 fatty acid confers albumin binding and heptamer formation [38]	Based on exenatide, but is modified by the deletion of one proline residue and addition of six lysine residues at the C-terminal [43]	GLP-1 dimer fused to albumin [44]	The GLP-1 portion of the molecule is fused to an IgG4 molecule, limiting renal clearance and prolonging activity [39]	Modifications designed to hinder cleavage by DPP-4 and by serine proteases and also allows greater receptor binding [45]
Half-life	2.4 h [46]	Half-life is an unpublished result but steady state concentrations at 6–7 weeks [47]	11–15 h [48]	2.7–4.3 h [49]	6–8 days [50]	≈5 days [39]	165 h [51]
T_{max}	2.1 h [46]	2.1–5.1 h during the first 48 h [47]	≈9–12 h [48]	1.25–2.25 h [49]	72–96 h [50]	24–72 h [39]	4, 6 and 8 h at 1, 8 and 30 mg doses, respectively [51]
Clearance	9.1 l/h [52]	Unpublished results	1.2 l/h [52]	21.2–28.5 l/h [49]	67 ml/h [53]	0.75 mg and 1.5 mg at steady state was 0.073 and 0.107 l/h, respectively [29]	Unpublished results
Antibody formation	• In head-to-head studies, antibodies were more common and titres were higher with exenatide once weekly compared with exenatide twice daily [54–56]. • Antibodies did not correlate with rates of reported AEs [54–56].		From six phase 3 studies, 8.7 and 8.3% of participants had low-titre antibodies to liraglutide 1.2 and 1.8 mg, respectively, after 26 weeks [57]	Antibodies developed in: • 56–60% of participants treated with 20 µg once daily [58] • 43% of participants treated with 10 µg once daily and 71% treated with 20 µg twice daily [59]	Antibodies developed in 3.7% of participants treated with albiglutide [14]	Dulaglutide antidrug antibodies in 1% of participants and dulaglutide neutralising antidrug antibodies in 1% of patients [13]	Detected in 49% of participants [40]

AE, adverse event; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GLP-1RA, GLP-1 receptor agonist; IgG4, immunoglobulin 4; T_{max}, time to maximum plasma concentration.
*Value based on similarity to exenatide.

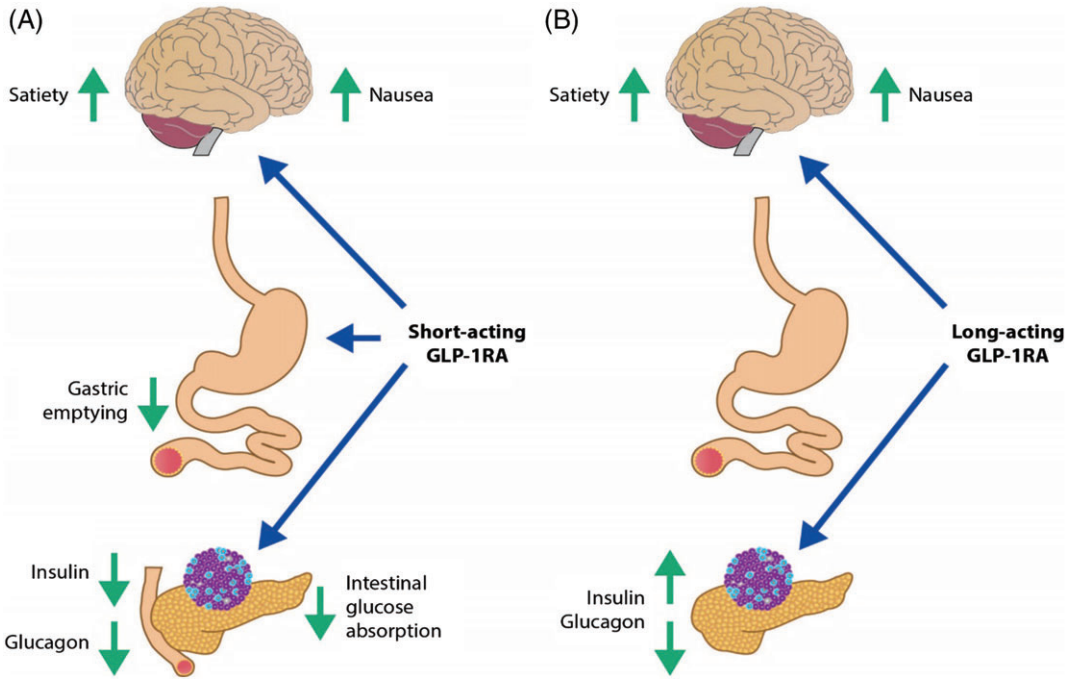

Figure 1. Gastric-emptying effects of short-acting versus longer-acting glucagon-like peptide-1 receptor agonists (GLP-1RAs). (A) Short-acting GLP-1RAs suppress gastric emptying, which prolongs the presence of food in the stomach and upper small intestine; the reduced transpyloric flow causes delayed intestinal glucose absorption and diminished postprandial insulin secretion. Short-acting GLP-1RAs may also directly suppress glucagon secretion. (B) Longer-acting GLP-1RAs do not significantly affect gastric motility, because of tachyphylaxis. Instead, longer-acting GLP-1RAs exert more of their effect via the pancreas, increasing insulin secretion, and inhibiting glucagon secretion via paracrine release of somatostatin. By targeting the central nervous system, both shorter- (A) and longer (B) -acting GLP-1RAs increase satiety and also may induce nausea. Adapted from Meier [22]. Adapted by permission from Macmillan Publishers Ltd: *Nature Reviews Endocrinology* 2012;8(12):728–42, copyright 2012.

the DURATION-6 and LEAD-6 studies, led to greater HbA1c reductions than both exenatide twice daily and once weekly ($p \leq 0.02$) [66,67]. Liraglutide also led to greater reductions in HbA1c than lixisenatide ($p < 0.01$) in the phase II study (although it was not the primary endpoint and the study duration was short [61]). Likewise, in the HARMONY 7 study [14], liraglutide led to greater reductions in HbA1c than albiglutide (however, the predefined non-inferiority criteria for albiglutide were not met). In the AWARD-6 study [13], the reduction in HbA1c did not differ between liraglutide and dulaglutide after 26 weeks of treatment. In the T-emerge 2 study, taspoglutide at 10 and 20 mg led to greater reductions in HbA1c than exenatide 10 µg twice daily ($p < 0.0001$) [40].

In addition, PPG and FPG were assessed in many of these trials. As expected, based on the delayed gastric emptying seen with the short-acting GLP-1RAs, exenatide twice daily and lixisenatide had greater effects on PPG than the longer-acting GLP-1RAs and this improvement was observed after the meal that followed the injection. For example, in the phase II study, lixisenatide administered before breakfast was associated with significantly greater reductions in maximum PPG excursion than liraglutide (−3.9 mmol/l vs −1.4 mmol/l, respectively; $p < 0.0001$), resulting in PPG of 7.3 and 10.1 mmol/l, respectively, 2 h after starting breakfast [61]. The differential effect on PPG is evident in the 24-h plasma glucose profiles shown in Figure 3. These data are supported by results from another phase II study, which showed that lixisenatide had a significantly greater effect than liraglutide in reducing area under the PPG curve after a standardized solid breakfast. This difference was thought to be attributable to significant delays in gastric emptying with lixisenatide versus liraglutide, which reduced post-breakfast blood glucose exposure [68].

Similarly, in a comparison of exenatide twice daily and exenatide once weekly, the mean change from baseline in 2-h PPG was significantly greater with the twice-daily versus the once-weekly formulation (−6.9 mmol/l vs −5.3 mmol/l, respectively; $p = 0.0124$), and the delay in gastric emptying was more pronounced with exenatide twice daily than with exenatide once weekly [54]. Furthermore, in a study conducted in Asian participants by Ji et al. [56], exenatide twice daily produced significantly greater reductions in postprandial blood glucose than exenatide once weekly based on assessments 2 h after each of the morning and evening meals ($p < 0.001$); however, in a sub-analysis of participants in the T-emerge 2 study, the longer-acting GLP-1RA taspoglutide had similar effects to exenatide twice daily on postprandial metabolism, although the mechanisms underlying this effect are not entirely clear [69].

Generally, the longer-acting GLP-1RAs improve glucose control via a downward shift of the whole 24-h glucose curve, which explains the greater overall efficacy compared with the short-acting exenatide twice daily and lixisenatide once daily. While the short-acting GLP-1RAs typically have an advantage with respect to PPG, the situation is reversed with FPG. Here, the longer-acting GLP-1RAs resulted in greater improvements.

Table 2. Design of published phase III (and one key phase II) randomized head-to-head studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes.

Study name	Treatment arms	Duration	Inclusion criteria	Primary endpoint	Key secondary endpoints
DURATION-1 [54]	Exenatide once weekly vs exenatide twice daily vs	30 weeks*	≥16 years of age Therapy with diet and exercise, or with 1–2 OADs (metformin, SU and/or TZD) HbA1c 7.1–11.0% FPG <16 mmol/l BMI 25–45 kg/m^2	Change in HbA1c	Participants achieving HbA1c targets [≤7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol) and ≤6.0% (42 mmol/mol)] Changes in FPG, PPG, weight, BP, lipids and glucagon Exenatide pharmacokinetics and paracetamol absorption Safety and tolerability
DURATION-5 [55]	Exenatide once weekly vs exenatide twice daily	24 weeks	≥18 years of age Treated with diet and exercise, or with metformin, SU, TZD or a combination HbA1c 7.1–11.0% FPG <15.5 mmol/l BMI 25–45 kg/m^2	Change in HbA1c	Participants achieving HbA1c targets [<7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol)] Patients achieving FPG target (≤7.0 mmol/l) Changes in FPG, weight, BP and lipids Safety and tolerability
Ji et al. [56]	Exenatide once weekly vs exenatide twice daily	26 weeks	≥20 years of age Treated with 1–3 OADs (metformin, SU, TZD) HbA1c 7.0–11.0% BMI 21–35 kg/m^2	Change in HbA1c	Participants achieving HbA1c targets [≤7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol) and ≤6.0% (42 mmol/mol)] Changes in FSG, SMPG, weight, lipids, HOMA-β and insulin sensitivity Safety and tolerability
DURATION-6 [67]	Exenatide once weekly vs liraglutide once daily	26 weeks	≥18 years of age Treated with diet and exercise and OADs (metformin, SU, metformin + SU, or metformin + pioglitazone) HbA1c 7.1–11.0% BMI ≤45 kg/m^2 Stable body weight	Change in HbA1c	Participants achieving HbA1c target (<7.0%) Changes in FSG, weight, BP and lipids Patient-reported outcomes Safety and tolerability
LEAD-6 [66]	Exenatide twice daily vs liraglutide once daily	26 weeks*	18–80 years of age Therapy with metformin, SU or both HbA1c 7.0–11.0% BMI ≤45 kg/m^2	Change in HbA1c	Participants reaching HbA1c targets [<7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol)] Changes in FPG, SMPG, weight, BP, lipids, glucagon and HOMA-β Safety and tolerability
GetGoal-X [12]	Exenatide twice daily vs lixisenatide once daily	24 weeks	21–84 years of age Treated with metformin HbA1c 7.0–10.0%	Change in HbA1c	Participants achieving HbA1c targets [<7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol)] Changes in FPG and weight Safety and tolerability

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