Differentiating between GLP-1 receptor agonists and DPP-4 inhibitors

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Article points

1. Dipeptidyl peptidase-4 inhibitors (DPP-4Is) inhibit the activity of DPP-4 to prolong the effects of native glucagon-like peptide-1 (GLP-1), whereas GLP-1 receptor agonists (GLP-1RAs) provide activation of the GLP-1 receptor while remaining resistant to degradation by DPP-4.
2. Both DPP-4Is and GLP-1RAs provide glycaemic control in people with type 2 diabetes, and GLP-1RAs are also associated with significant weight loss.
3. Differences between DPP-4Is and GLP-1RAs include efficacy, tolerability, mechanism of action, and administration route. Reductions in HbA_{1c} and weight are generally greater with GLP-1RAs.

Key words

- DPP-4 inhibitors
- GLP-1 receptor agonists
- Type 2 diabetes

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Concerns about the adverse effects associated with many "traditional" blood glucose lowering therapies for type 2 diabetes, including weight gain and risk of hypoglycaemia, as well as increasing awareness of blood glucose regulation processes, has led to the emergence of newer therapies. Incretin therapies, including dipeptidyl peptidase-4 inhibitors (DPP-4Is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), utilise different mechanisms to increase levels of GLP-1, which is an incretin hormone secreted by the gastrointestinal system in response to food intake. Research has shown that both types of incretin therapy provide significant reductions in hyperglycaemia and are useful options for individualised treatment regimens. This article provides an overview of the older, "traditional" therapies and describes some key differences between newer incretin therapies.

Type 2 diabetes is a progressive disease associated with macrovascular and microvascular comorbidities. Worldwide, approximately 382 million people have diabetes, and this is expected to increase to 592 million by 2035 (International Diabetes Federation [IDF], 2013).

When considering the management of type 2 diabetes, various UK, European and US guidelines (NICE, 2009; Handelsman et al, 2011; Inzucchi et al, 2012; Garber et al, 2013) recommend early, ongoing dietary improvement and increased physical activity, alongside diabetes education. As diet and exercise usually become inadequate within a year, and HbA_{1c} levels start to rise (Nathan et al, 2009), step-wise treatment intensification is needed to restore HbA_{1c} to target levels (NICE, 2009; Inzucchi et al, 2012).

After starting oral antidiabetes drug (OAD) monotherapy, typically metformin, dual and later triple therapy may be added. The addition of insulin may be required if hyperglycaemia continues. Current guidelines stress the importance of individualising treatment, balancing glucose lowering with risk of hypoglycaemia and other adverse effects.

Traditional therapies

Traditional OADs, such as metformin, sulphonylureas (SUs) or thiazolidinediones (TZDs), and insulin can normalise blood glucose levels, but may lead to limiting adverse events (Pi-Sunyer, 2009; Pollack et al, 2010): SUs and insulin are associated with a risk of hypoglycaemia; metformin and alpha-glucosidase inhibitors may produce gastrointestinal disturbances; TZDs can lead to oedema; SUs, glinides, TZDs and insulin are associated with weight gain (Rodbard et al, 2009). Options may also be limited by disease. For example, metformin and TZDs are contraindicated in some people with heart failure and metformin in people with renal disease (Rodbard et al, 2009).

Given these limitations, the emergence of incretin therapies is encouraging. Oral dipeptidyl peptidase-4 inhibitors (DPP-4Is) and injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) stimulate insulin release and inhibit glucagon secretion in a glucose-dependent manner and are therefore associated with a low inherent risk of hypoglycaemia (Inzucchi et al, 2012). Furthermore, they demonstrate weight neutrality (DPP-4Is) or weight loss (GLP-1RAs) and data suggest modest benefits on some cardiovascular risk factors (Mudaliar and Henry, 2009; Monami et al, 2013; 2014).

GLP-1 and the incretin system in type 2 diabetes

GLP-1 is a major incretin hormone secreted by the gastrointestinal system in response to food intake (Holst et al, 2009). Insulin produced after eating is partly stimulated by this hormone (Nauck et al, 1986a; 1986b) within the "incretin response" – where insulin secretion is greater following an oral rather than intravenous glucose load, despite similar plasma glucose levels (*Figure 1*). GLP-1 also contributes to feelings of fullness, which reduce energy intake and promote weight loss. However, native GLP-1 has a half-life of <2 minutes (Vilsboll et al, 2003), and is therefore impractical as a therapeutic agent.

Incretin therapies: Overview and mechanism of action

DPP-4Is and GLP-1RAs both increase the effects of GLP-1. DPP-4Is inhibit the activity of the enzyme, DPP-4, which rapidly degrades GLP-1, in order to prolong the effects of native GLP-1. GLP-1RAs provide activation of the GLP-1 receptor while remaining resistant to degradation by DPP-4.

Several incretin-based therapies have been approved for use. Four GLP-1RAs (exenatide, exenatide extended release, liraglutide, and lixisenatide) are available. There are now five DPP-4Is available (sitagliptin, saxagliptin, vildagliptin, linagliptin and alogliptin).

Exenatide shows 53% amino-acid similarity to native GLP-1 (Chen and Drucker, 1997), but is resistant to breakdown by DPP-4 and therefore has a half-life of 2–4 hours, necessitating twice-daily (BD) injection. The long-acting release formulation of exenatide allows once-weekly (OW) dosing (electronic Medicines Compendium [eMC], 2014a).

Liraglutide is a human GLP-1RA with 97% homology to native GLP-1 (Knudsen et al, 2000). Liraglutide is administered by subcutaneous injection, where it self-associates into heptamers resulting in delayed absorption (Steensgaard et al, 2008). With a half-life of 11–15 hours, liraglutide is administered once

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1. Glucagon-like peptide-1 (GLP-1) is a major incretin hormone secreted by the gastrointestinal system in response to food intake. Insulin produced after eating is partly stimulated by this hormone.
2. Dipeptidyl peptidase-4 inhibitors (DPP-4Is) and GLP-1 receptor agonists (GLP-1 RAs) both increase the effects of GLP-1. DPP-4Is inhibit the activity of the enzyme, DPP-4, which rapidly degrades GLP-1, in order to prolong the effects of native GLP-1. GLP-1RAs provide activation of the GLP-1 receptor while remaining resistant to degradation by DPP-4.
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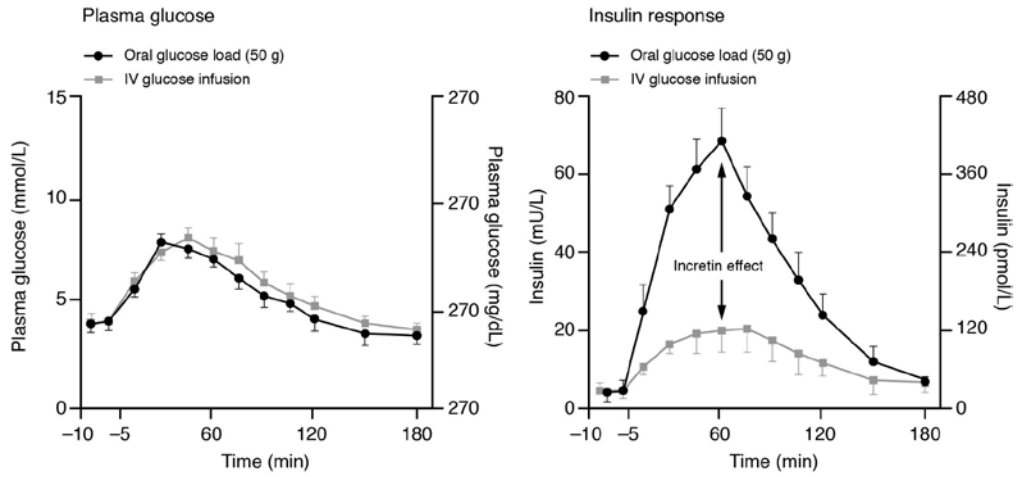

Figure 1. The incretin effect. Reproduced with permission from Nauck et al (1986b).

Table 1. Summary of HbA_{1c} and weight changes in incretin therapy trials.

Reference (study)	Therapies compared	HbA_{1c} change from baseline (%)	Weight change from baseline (kg)
Comparison of currently available DPP-4 inhibitors			
Scheen et al, 2010	Saxagliptin 5 mg OD Sitagliptin 100 mg OD	–0.5 –0.6 (NS)	0.4 0.4 (NS)
Li et al, 2014	Vildagliptin Saxagliptin Sitagliptin	–1.3 –1.2 –1.1 (NS)	- - -
Comparison of currently available GLP-1 receptor agonists			
Blevins et al, 2011 (DURATION-5)	Exenatide 2 mg OW Exenatide 10 µg BD	–1.6 –0.9 (*P*<0.0001)	–2.3 –1.4 (NS)
Buse et al, 2009 (LEAD-6)	Liraglutide 1.8 mg OD Exenatide 10 µg BD	–1.1 –0.6 (*P*<0.0001)	–3.2 –2.9 (NS)
Buse et al, 2013 (DURATION-6)	Liraglutide 1.8 mg OD Exenatide 2 mg OW	–1.5 –1.3 (*P*=0.002)	–3.6 –2.7 (*P*=0.0005)
Drucker et al, 2008 (DURATION-1)	Exenatide 2 mg OW Exenatide 10 µg BD	–1.9 –1.5 (*P*=0.0023)	–3.7 –3.6 (NS)
Rosenstock et al, 2013 (GetGoal-X)	Lixisenatide 20 µg OD Exenatide 10 µg BD	–0.8 –1.0 (NS)	–2.8 –3.8 (NS)
Comparison of DPP-4 inhibitors and GLP-1 receptor agonists			
Bergenstal et al, 2010 (DURATION-2)	Exenatide 2 mg OW Sitagliptin 100 mg OD	–1.5 –0.9 (*P*<0.0001)	–2.3 –0.8 (*P*=0.0002)
Pratley et al, 2010 (LIRA-DPP-4)	Liraglutide 1.8 mg OD Liraglutide 1.2 mg OD Sitagliptin 100 mg OD	–1.5 –1.2 –0.9 (*P*<0.0001)	–3.4 –2.9 –1.0 (*P*<0.0001)
Russell-Jones et al, 2012 (DURATION-4)	Exenatide 2mg OW Sitagliptin 100mg OD	–1.5 –1.2 (*P*<0.001)	–2.0 –0.8 (*P*<0.001)

Non-incretin comparators are not listed. BD=twice daily; OD=once daily; OW=once weekly; NS=not significant

daily (OD; Elbrond et al, 2002; eMC, 2014b).

Lixisenatide is a synthetic GLP-1RA, a 44-amino-acid peptide that differs from exendin-4 (a peptide produced exclusively by the salivary glands of the Gila monster [*Heloderma suspectum*]) by the addition of six lysine residues and the deletion of one proline at the C-terminal (Werner et al, 2010). The elimination half-life of lixisenatide is approximately 2–4 hours (Barnett, 2011) but, unlike exenatide, it is administered once-daily (eMC, 2014c) as the once-daily regimen gave the best balance of efficacy and tolerability in clinical trials (Ratner et al, 2010).

DPP-4 is a cell-surface aminopeptidase enzyme that degrades some gastrointestinal hormones, neuropeptides, cytokines and chemokines (Drucker and Nauck, 2006). The DPP-4Is are reversible, competitive inhibitors of DPP-4 and inhibit approximately 80–90% of DPP-4 activity (Forst et al, 2011; Herman et al, 2005; He et al, 2007), leading to a 2–3-fold elevation in GLP-1 (Herman et al, 2005; Mari et al, 2005). The half-life of 3–21 hours allows OD (saxagliptin, sitagliptin, linagliptin, alogliptin [eMC, 2014d,e,f,g]) or BD (vildagliptin) regimens (eMC, 2014h), administered orally.

Efficacy and safety of GLP-1RAs and DPP-4 inhibitors

Comparison of currently available GLP-1 RAs

Several trials have directly compared the two classes of incretin therapy (*Table 1*). At the time of writing, five such trials compared different GLP-1RAs. In the LEAD-6 study, liraglutide led to significantly greater reductions in HbA_{1c} and fasting plasma glucose (FPG) versus exenatide, with similar reductions in weight and systolic blood pressure (SBP; Buse et al, 2009). In an extension phase, patients switched from exenatide to liraglutide experienced additional reductions in HbA_{1c}, FPG, weight and SBP (Buse et al, 2010a). Both agents were well-tolerated, with significantly less ongoing nausea in liraglutide- (3%) versus exenatide-treated patients (9%) at 26 weeks (*P*<0.0001). Minor hypoglycaemia was significantly less frequent with liraglutide (1.93 versus 2.60 events/patient-year; *P*=0.01, Buse et al, 2009).

In a 26-week study comparing liraglutide (1.8 mg OD) with exenatide 2 mg OW (Buse et al, 2013), liraglutide led to greater reductions in $HbA_{1c,}$ weight and SBP, although gastrointestinal adverse events were more common in the liraglutide group (21% versus 9% in exenatide group). Hypoglycaemia rates were similar between groups (12% in the liraglutide group and 15% in the exenatide group for people taking concomitant SU, and 3% in the liraglutide group and in 4% in the exenatide group for those without concomitant SU).

In a 24-week study comparing lixisenatide to exenatide BD, both led to reductions in HbA_{1c} and weight, with lixisenatide associated with lower levels of symptomatic hypoglycaemia (2.5 versus 7.9%; $P<0.05$) and nausea (24.5 versus 35.1%; $P<0.05$; Rosenstock et al, 2013).

Three studies (Drucker et al, 2008; Buse et al, 2010b; Blevins et al, 2011) compared formulations of exenatide (*Table 1*). After 30 weeks in DURATION-1, exenatide OW led to significantly greater reductions in HbA_{1c} and FPG compared with exenatide BD, and more people reached HbA_{1c} ≤53 mmol/mol (77% versus 61%; $P=0.004$). Reductions in weight were similar. The most commonly reported adverse event was nausea, occurring in fewer people taking exenatide OW (26.4% versus 34.5%). Rates of minor hypoglycaemia were very low in both groups (0% and 1.1%), occurring predominantly in people taking SUs (14.5% and 15.4%). Improvements were maintained in people continuing exenatide OW for a further 22 weeks; those who switched from BD to OW exenatide saw additional HbA_{1c} reductions. Glycaemic and weight benefits were maintained in people continuing treatment for 2 years, and SBP and lipid profiles significantly improved. Nausea frequency decreased over time, and was generally mild.

In the 24-week DURATION-5 study, mean HbA_{1c} reductions were less than in DURATION-1, but consistent with previous studies (Buse et al, 2004; DeFronzo et al, 2005; Heine et al, 2005; Kendall et al, 2005; Bergenstal et al, 2010; Diamant et al, 2010).

Overall, in these trials, exenatide OW and liraglutide appeared to outperform exenatide BD in terms of glucose-lowering efficacy, and gastrointestinal tolerability was better with exenatide OW than with liraglutide or exenatide BD. One point of note is that in these trials, liraglutide was used at a dose of 1.8 mg, which is not currently recommended by NICE (NICE, 2010).

The development of antibodies during treatment can be associated with reduced efficacy (Berntorp et al, 2006) or adverse events (Jahn and Schneider, 2009). Exenatide appears to be more immunogenic than liraglutide, and the limited antibody response with liraglutide does not affect glycaemic efficacy or treatment safety (Buse et al, 2011).

Comparison of currently available DPP-4Is

Two trials have compared DPP-4Is: saxagliptin 5 mg OD versus sitagliptin 100 mg OD, both in addition to metformin (Scheen et al, 2010) and 5 mg saxagliptin OD versus 100 mg sitagliptin OD versus 50 mg vildagliptin BD, each in addition to metformin and another oral hypoglycemic agent (Li et al, 2014). Their efficacy and incidences of adverse events were similar (*Table 1*).

Comparisons of currently available GLP-1RAs and DPP-4Is

In a comparison of exenatide OW versus sitagliptin (Bergenstal et al, 2010; *Table 1*), reductions in HbA_{1c} and weight loss were greater with exenatide OW. The most frequent adverse events with exenatide OW and sitagliptin were nausea (24% and 10%) and diarrhoea (18% and 10%, respectively). During a 26-week extension, people switched from sitagliptin to exenatide OW experienced significant further improvements in HbA_{1c} (reductions of 3 mmol/mol [0.3%]), FPG (0.7 mmol/L) and weight (–1.1 kg; Wysham et al, 2011). In another 26-week trial (DURATION-4), exenatide OW led to significantly greater changes in HbA_{1c} and weight compared with sitagliptin 100 mg (Russell-Jones et al, 2012).

There has been one large trial comparing liraglutide with a DPP-4I (Pratley et al, 2010; *Table 1*). Combined with metformin, liraglutide 1.2 mg or 1.8 mg led to greater changes in

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1. Overall, in the DURATION-1 and DURATION-5 trials, exenatide OW and liraglutide appeared to outperform exenatide BD in terms of glucose-lowering efficacy, and gastrointestinal tolerability was better with exenatide OW than with liraglutide or exenatide BD.
2. Two trials have compared DPP-4Is and found that efficacy and incidences of adverse events were similar.
3. Patient-reported outcome (PRO) data from one trial showed that treatment satisfaction was greater among people in a liraglutide 1.8 mg group compared to a sitaglipin group but similar for liraglutide 1.2 mg and sitagliptin groups.

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1. A comparison of PRO outcomes in the DURATION-2 study found that improvements in weight-related quality of life scores with exenatide OW and sitagliptin correlated with change in body weight and that general health scores increased in people in the exenatide OW and sitagliptin groups.
2. In the DURATION-1 study, people in exenatide OW and BD groups showed similar improvements in treatment satisfaction and weight-related quality of life after 30 weeks of treatment.
3. Incretin-based therapies appear to be well received by patients, and these data discussed above suggest that the injectable administration route is not a barrier to GLP-1RAs, as is the case for insulin.
4. GLP-1RAs are administered by subcutaneous injection: liraglutide OD and exenatide OW at any time of day and exenatide BD and lixisenatide OD within 60 minutes before meals. DPP-4Is are administered orally, either OD (saxagliptin, sitagliptin, linagliptin, alogliptin) or BD (vildagliptin).

HbA_{1c}, FPG and weight loss versus sitagliptin, which were maintained at 52 weeks (Pratley et al, 2011).

Patient-reported outcome comparison studies

Patient-reported outcome (PRO) data can provide useful insight into individuals' experiences. A comparison of liraglutide and exenatide BD showed similar, high baseline treatment satisfaction (TS) for both (Schmidt et al, 2011). At 26 weeks, Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores increased more with liraglutide compared with exenatide (4.71 versus 1.66 points; $P<0.0001$), and liraglutide-treated patients perceived a greater reduction in hypoglycaemia on the DTSQ change version (DTSQc), but not DTSQ status version (DTSQs; DTSQc: between-treatment difference=0.48; $P=0.02$), and hyperglycaemia (DTSQc: between-treatment difference=0.74; $P=0.001$). Significantly more people in the liraglutide group (91% versus 82%; $P=0.02$) expressed TS (DTSQs >24). During a 26-week extension, TS increased significantly ($P=0.003$ at week 40) in people switching to liraglutide.

In a patient subgroup from a liraglutide versus sitagliptin trial (Davies et al, 2011), overall TS improvement was greater with liraglutide 1.8 mg versus sitagliptin ($P=0.03$), and similar between sitagliptin and liraglutide 1.2 mg. In a 26-week extension, a greater increase in DTSQ score was reported with liraglutide 1.8 mg versus sitagliptin ($P=0.03$; Pratley et al, 2011).

Among sitagliptin-treated people switched to liraglutide 1.2 mg or 1.8 mg, overall DTSQ score increased compared with baseline (liraglutide 1.2 mg group, $P=0.02$; Pratley et al, 2012), although there was a transient increase in gastrointestinal reactions. In this trial, participants originally randomised to receive liraglutide continued unchanged.

A comparison of PRO outcomes for exenatide, sitagliptin and pioglitazone in the DURATION-2 study found that IWQOL-Lite (Impact of Weight on Quality of Life) scores had increased significantly in both the exenatide OW and sitagliptin treatment arms (both $P<0.05$) and there were no statistically significant differences between the exenatide QW and sitagliptin groups in total weight-related quality of life. General health utility, measured using EQ-5D (EuroQol 5 Dimensions measure), also increased in people in the exenatide OW and sitagliptin groups ($P<0.05$; Best et al, 2011). All groups experienced significant improvements on the psychological well-being global scale and all six domain scores. All groups experienced significant improvements in total diabetes treatment satisfaction scores and the exenatide OW group experienced greater improvement than the sitagliptin group in treatment satisfaction total scores. In this trial, nausea and vomiting reported with exenatide did not reduce patient satisfaction.

In the DURATION-1 study (Drucker et al, 2008), people in exenatide OW and BD groups showed similar improvements in treatment satisfaction and weight-related quality of life after 30 weeks of treatment (Best et al, 2009). However, DTSQ items related to "perceived frequency of hyperglycaemia" and "willingness to continue current treatment" were significantly higher in the exenatide OW group. Participants who switched from exenatide BD to exenatide OW after 30 weeks reported further improvements in treatment satisfaction.

Incretin-based therapies appear to be well received by patients, and these data discussed above suggest that the injectable administration route is not a barrier to GLP-1RAs, as is the case for insulin.

Dosage and administration

GLP-1RAs are administered by subcutaneous injection: liraglutide OD and exenatide OW at any time of day (eMC, 2014a,b), and exenatide BD and lixisenatide OD within 60 minutes before meals (eMC, 2014c,i). Exenatide OW requires mixing and syringe preparation using a single-dose kit, so healthcare professionals should ensure that individuals receive the appropriate education. The DPP-4Is are administered orally, either OD (saxagliptin, sitagliptin, linagliptin, alogliptin) or BD (vildagliptin). They do not need to be taken with food.

Therapeutic experience is limited in special

patient groups for both GLP-1RAs and DPP-4Is. In people aged >75 years, no dose adjustment is recommended, although escalation with exenatide BD should be done cautiously. For linaglitpin, clinical experience for people >80 years is lacking so caution must also be exercised. None is recommended for patients aged <18 years (see Summary of Product Characteristics [SPC] for each product). Exenatide is cleared renally (Linnebjerg et al, 2007), and hence dose escalation should be performed prudently in people with moderate renal impairment. Exenatide BD and lixisenatide are not recommended in severe renal impairment (eMC, 2014b,i); exenatide OW is not recommended in moderate or severe renal impairment (eMC, 2014a). Liraglutide is not renally excreted but, due to limited therapeutic evidence, it currently can not be recommended for use in people with moderate or severe renal impairment in the UK (eMC, 2014b) but it is approved in the US to be used with caution at all stages of renal disease (Novo Nordisk, 2013). Exenatide BD, lixisenatide and liraglutide are indicated for use as adjunctive therapy to basal insulin (eMC 2014c,i,j).

With saxagliptin, sitagliptin, and vildagliptin, dosing adjustment is required in moderate and severe renal impairment, as these compounds are largely renally excreted and drug accumulation has been reported (see SPC for specific products). Linagliptin is mostly excreted non-renally and can be used at all stages of renal disease (eMC, 2014f). Therefore, DPP-4 inhibitors may be a more appropriate choice for patients with moderate or severe renal impairment. However, safety of liraglutide in this population has been demonstrated (Idorn et al, 2014; Umpierrez et al, 2014).

Safety and tolerability

Both classes of incretin therapy are generally well tolerated. Furthermore, due to their glucose-dependent mechanism of action, hypoglycaemia rates are low when these agents are not combined with insulin or an insulin secretagogue.

The most common side effects of GLP-1RAs are gastrointestinal. Nausea is more common with GLP-1RAs than DPP-4Is, but tends to be mild and transient (Bergenstal et al 2010; Pratley et al, 2010; Russell-Jones et al, 2012). Among GLP-1RAs, head-to-head studies found a lower incidence of nausea with liraglutide and lixisenatide (compared with exenatide BD; Buse et al 2009; Rosenstock et al, 2013) and exenatide OW (compared with exenatide BD or liraglutide; Drucker et al, 2008, Buse et al, 2013).

Concerns have been raised regarding the risk of pancreatitis with incretin therapies; however, an assessment by the European Medicines Agency (EMA) has concluded that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer are inconsistent with the current clinical data (EMA, 2013). All SPCs for DDP-4Is and GLP-1RAs advise informing patients of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain and these agents are contraindicated in people with a history of pancreatitis. Both DPP-4Is and GLP-1RAs should be discontinued if pancreatitis is suspected.

Recently, the first few of several cardiovascular outcome trials required by regulatory agencies for DPP-4Is have reported results. In the EXAMINE trial, carried out in patients with type 2 diabetes who had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with alogliptin compared with placebo (White et al, 2013). In the SAVOR-TIMI trial, people with type 2 diabetes who had a history of, or were at risk for, cardiovascular events found no change in the rate of ischemic events, but an increase in hospitalisation for heart failure with saxagliptin (Scirica et al, 2013). There are no data available as yet for ongoing trials with GLP-1RAs.

Practical considerations

Potential advantages of DPP-4Is are less frequent nausea and oral administration. Nausea with GLP-1RAs typically occurs early and can be lessened with an incremental dosing approach, where possible. Injecting at meal times and eating smaller meals may decrease nausea; returning to a lower GLP-1RA dose for a week and repeating incremental dosing is another

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2. Cardiovascular outcome trials for alogliptin showed that among people with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo. In the trial for saxagliptin, results showed that it did not increase or decrease the rate of ischemic events, though the rate of hospitalisation for heart failure was increased.
3. Potential advantages of DPP-4Is are less frequent nausea and oral administration. Nausea with GLP-1RAs typically occurs early and can be lessened with an incremental dosing approach, where possible.

"Differences between DPP-4Is and GLP-1RAs include efficacy, tolerability, mechanism of action, and administration route."

option, where possible (Unger and Parkin, 2011; Novo Nordisk, 2013). Practical demonstration and patient education is important to allay injection fears. Although GLP-1RAs are more expensive than DPP-4Is in pure cost, cost-utility analyses make the situation more complex due to differences in efficacy, and GLP-1RAs have been found to be comparable or better in some health-economic analyses (Lage et al, 2009; Davies et al, 2012). GLP-1RAs may be a better choice when adding therapy to people close to target (King et al, 2013) due possibly to superphysiological levels of GLP-1 activation.

Conclusion

Differences between DPP-4Is and GLP-1RAs include efficacy, tolerability, mechanism of action, and administration route. GLP-1RAs yield higher levels of GLP-1 than DPP-4Is, which may account for increased anti-hyperglycaemic and weight benefits and increased GI side effects. Reductions in HbA_{1c} and weight are generally greater with GLP-1RAs.

PRO data suggest that patient acceptance of injectables is not a major problem, and GLP-1RAs are actually associated with greater TS compared to other anti-diabetes drugs. Both types of incretin therapies provide a low risk of hypoglycaemia when not used in combination with insulin or insulin secretagogues. Nausea is common with GLP-1RAs, but tends to be transient and should be considered in the context of HbA_{1c} improvements and weight loss. Treatments should be tailored to individual patients, based on their specific needs, comorbidities, and adverse effects with different therapies, and cost considerations should be taken into account. ■

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Barnett AH (2011) Lixisenatide: Evidence for its potential use in the treatment of type 2 diabetes. *Core Evid* **6**: 67–79

Bergenstal RM, Wysham C, MacConell L et al (2010) Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2) *Lancet* **376**: 431–9

Berntorp E, Shapiro A, Astermark J et al (2006) Inhibitor treatment in haemophilias A and B. *Haemophilia* **12**(Suppl 6): 1–7

Best JH, Boye KS, Rubin RR et al (2009) Improved treatment satisfaction and weight-related quality of life with exenatide once weekly or twice daily. *Diabet Med* **26**: 722–8

Best JH, Rubin RR, Peyrot M et al (2011) Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. *Diabetes Care* **34**: 314–9

Blevins T, Pullman J, Malloy J et al (2011) DURATION-5: Exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metabol* **96**: 1301–10

Buse JB, Henry RR, Han J et al (2004) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* **27**: 2628–35

Buse J, Rosenstock J, Sesti G et al (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes. *Lancet* **374**: 39–47

Buse J, Sesti G, Schmidt WE et al (2010a) Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care* **33**: 1300–3

Buse JB, Drucker DJ, Taylor KL et al (2010b) DURATION-1 Study Group. DURATION-1. *Diabetes Care* **33**: 1255–61

Buse JB, Garber A, Rosenstock J et al (2011) Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events. *J Clin Endocrinol Metabol* **96**: 1695–702

Buse JB, Nauck M, Forst T et al (2013) Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): A randomised, open-label study. *Lancet* **381**: 117–24

Chen YE, Drucker DJ (1997) Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. *J Biol Chem* **72**: 4108–15

Davies M, Pratley R, Hammer M et al (2011) Liraglutide improves treatment satisfaction in people with type 2 diabetes compared with sitagliptin, each as an add on to metformin. *Diabet Med* **28**: 333–7

Davies MJ, Chubb BD, Smith IC, Valentine WJ (2012) Cost-utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in type 2 diabetes mellitus. *Diabet Med* **29**: 313–20

DeFronzo RA, Ratner RE, Han J et al (2005) Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* **28**: 1092–100

Diamant M, Van Gaal L, Stranks et al (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION- 3). *Lancet* **375**: 2234–43

Drucker DJ, Nauck MA (2006) The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* **368**: 1696–705

Drucker DJ, Buse JB, Taylor K et al (2008) Exenatide once weekly versus twice daily for the treatment of type 2 diabetes. *Lancet* **372**: 1240–50

Elbrond B, Jakobsen G, Larsen S et al (2002) Pharmacokinetics, pharmacodynamics, safety, and tolerability of a single-dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male subjects. *Diabetes Care* **25**: 1398–404

Electronic Medicines Compendium (2014a) Exenatide Bydureon. EMC. Available at: http://bit.ly/1wxLtP9 (accessed 10.12.14)

Electronic Medicines Compendium (2014b) Liraglutide. eMC, Surrey. Available at: http://bit.ly/1BypcSx (accessed 10.12.14)

Electronic Medicines Compendium (2014c) Lixisenatide. eMC, Surrey. Available at: http://bit.ly/1Cpv6Ej (accessed 10.12.14)

Electronic Medicines Compendium (2014d) Saxagliptin. eMC, Surrey. Available at: http://bit.ly/1wcYL1n (accessed 10.12.14)

Electronic Medicines Compendium (2014e) Sitagliptin. eMC, Surrey. Available at: http://bit.ly/1vDYK1v (accessed 10.12.14)

Electronic Medicines Compendium (2014f) Linagliptin. eMC, Surrey. Available at: http://bit.ly/1IzKcKy (accessed 10.12.14)

Electronic Medicines Compendium (2014g) Alogliptin. eMC, Surrey. Available at: http://bit.ly/1wxMDKm (accessed 10.12.14)

Electronic Medicines Compendium (2014h) Vildagliptin. eMC, Surrey.

Available at: http://bit.ly/1yyvcta (accessed 10.12.14)
Electronic Medicines Compendium (2014i) Exenatide Byetta. eMC, Surrey. Available at: http://bit.ly/1ByqsVP (accessed 10.12.14)
Electronic Medicines Compendium (2014j) Levemir. eMC, Surrey. Available at: http://bit.ly/1vOoPA2 (accessed 10.12.14)
European Medicines Agency (2013) Assessment report for GLP-1 based therapies. EMA. Available at: http://bit.ly/1tbl9Il (accessed 21.10.14)
Forst T, Uhlig-Laske B, Ring A et al (2011) The oral DPP-4 inhibitor linagliptin significantly lowers HbA1c after 4 weeks of treatment in patients with type 2 diabetes mellitus. *Diabetes Obes Metabol* **13**: 542–50
Garber AJ, Abrahamson MJ, Barzilay JI et al (2013) AACE comprehensive diabetes management algorithm. *Endocr Pract* **19**: 327–36
Handelsman Y, Mechanick JI, Blonde L et al, AACE Task Force for Developing Diabetes Comprehensive Care Plan (2011) American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract* **17**(Suppl 2): 1–53
He YL, Serra D, Wang Y et al (2007) Pharmacokinetics and pharmacodynamics of vildagliptin in patients with type 2 diabetes mellitus. *Clinic Pharmacokinet* **46**: 577–88
Heine RJ, Van Gaal LF, Johns D et al (2005) Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* **143**: 559–69
Herman GA, Stevens C, Van Dyck K et al (2005) Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. *Clinic Pharmacol Therapeut* **78**: 675–88
Holst JJ, Vilsbøll T, Deacon CF (2009) The incretin system and its role in type 2 diabetes mellitus. *Mol Cell Endocrinol* **297**: 127–36
Idorn T, Knop FK, Jørgensen MB et al (2014) Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease. *Diabetologia* **57**(Suppl 1): 370, Abstract 909 (Poster)
International Diabetes Federation (2013) Diabetes Atlas. Available at: http://www.idf.org/diabetesatlas (accessed 10.12.14)
Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **35**: 1364–79
Jahn EM, Schneider CK (2009) How to systematically evaluate immunogenicity of therapeutic proteins. *Nat Biotechnol* **25**: 280–6
Kendall DM, Riddle MC, Rosenstock J et al (2005) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* **28**: 1083–91
King AB, Montanya E, Pratley RE et al (2013) Liraglutide achieves A_{1c} targets more often than sitagliptin or exenatide when added to metformin in patients with type 2 diabetes and a baseline A_{1c} <8.0%. *Endocr Pract* **19**: 64–72
Knudsen LB, Nielsen PF, Huusfeldt PO et al (2000) Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* **43**: 1664–9
Lage MJ, Fabunmi R, Boye KS, Misurski DA (2009) Comparison of costs among patients with type 2 diabetes treated with exenatide or sitagliptin therapy. *Advances in Therapy* **26**: 217–29
Li CJ, Liu XJ, Bai L et al (2014) Efficacy and safety of vildagliptin, saxagliptin or sitagliptin as add-on therapy in Chinese patients with type 2 diabetes inadequately controlled with dual combination of traditional oral hypoglycemic agents. *Diabetol Metab Syndr* **31**: 69
Linnebjerg H, Kothare PA, Park S et al (2007) Effect of renal impairment on the pharmacokinetics of exenatide. *Br J Clin Pharmacol* **64**: 317–27
Mari A, Sallas WM, He YL et al (2005) Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. *J Clin Endocrinol Metabol* **90**: 4888–94
Monami M, Ahren B, Dicembrini I, Mannucci E (2013) Dipeptidly peptidase-4 inhibitors and cardiovascular risk. *Diabetes Obes Metab* **15**: 112–20
Monami M, Dicembrini I, Nardini C et al (2014) Effects of glucagon-like peptide-1 agonists on cardiovascular risk. *Diabetes Obes Metab 16*: 38–47
Mudaliar S, Henry R (2009) Incretin therapies: Effects beyond glycemic control. *Am J Med* **122**(Suppl 6): S25–36
Nathan D, Buse J, Davidson M et al (2009) Medical management of hyperglycemia in type 2 diabetes. *Diabetes Care* **32**: 193–203
Nauck MA, Homberger E, Siegel EG et al (1986a) Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab* **63**: 492–8
Nauck M, Stockmann F, Ebert R, Creutzfeldt W (1986b) Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* **29**: 46–52.
NICE (2009) Type 2 diabetes: The management of type 2 diabetes CG87. Available at: www.nice.org.uk/cg87 (accessed 10.12.14)
NICE (2010) Liraglutide for the treatment of type 2 diabetes mellitus. TA203. Available at: www.nice.org.uk/ta203 (accessed 10.12.14)
Novo Nordisk (2013) Victoza Prescribing Information. Novo Nordisk. Available at: http://www.novo-pi.com/victoza.pdf (accessed 22.10.14)
Pi-Sunyer FX (2009) The impact of weight gain on motivation, compliance, and metabolic control in patients with type 2 diabetes mellitus. *Postgrad Med* **121**: 94–107
Pollack MF, Purayidathil FW, Bolge SC, Williams SA (2010) Patient-reported tolerability issues with oral antidiabetic agents. *Diab Res Clin Pract* **87**: 204–10
Pratley RE, Nauck M, Bailey T et al (2010) Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin. *Lancet* **375**: 1448–56
Pratley R, Nauck M, Bailey T et al (2011) One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes. *Int J Clin Pract* **65**: 397–407
Pratley RE, Nauck MA, Bailey T et al (2012) Efficacy and safety of switching from the DPP-4 inhibitor sitagliptin to the human GLP-1 analog liraglutide after 52 weeks in metformin-Treated patients with type 2 diabetes. *Diabetes Care* **35**: 1986–93
Ratner RE, Rosenstock J, Boka G (2010) Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. *Diabet Med* **27**: 1024–32
Rodbard HW, Jellinger PS, Davidson JA et al (2009) Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* **15**: 540–59
Rosenstock J, Raccah D, Korányi L et al (2013) Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin. *Diabetes Care* **36**: 2945–51
Russell-Jones D, Cuddihy RM, Hanefeld M et al, DURATION-4 Study Group (2012) Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4). *Diabetes Care* **35**: 252–8
Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A et al (2010) Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes/Metabol Res Rev* **26**: 540–9
Schmidt WE, Christiansen JS, Hammer M et al (2011) Patient-reported outcomes are superior in patients with Type 2 diabetes treated with liraglutide as compared with exenatide, when added to metformin, sulphonylurea or both. *Diabet Med* **28**: 715–23
Scirica BM, Bhatt DL, Braunwald E et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**: 1317–26
Steensgaard DB, Thomsen JK, Olsen HB, Knudsen LB (2008) The molecular basis for the delayed absorption of the once-daily human GLP-1 analogue, liraglutide. *Diabetes* **57** (Suppl 1): A164
Umpierrez G, Atkin S, Bain S (2014) Efficacy and safety of liraglutide versus placebo in subjects with type 2 diabetes and moderate renal impairment (LIRA-RENAL). *Diabetologia* **57**(Suppl 1):Abstract 182
Unger JR, Parkin CG (2011) Glucagon-like peptide-1 (GLP-1) receptor agonists: Differentiating the new medications. *Diabetes Ther* **2**: 29–39
Vilsboll T, Agersø H, Krarup T, Holst JJ (2003) Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. *Clin Endocrinol Metabol* **88**: 220–4
Werner U, Haschke G, Herling AW, Kramer W (2010) Pharmacological profile of lixisenatide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. *Regul Pept* **164**: 58–64
White WB, Cannon CP, Heller SR (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**: 1327–35
Wysham C, Bergenstal R, Malloy J et al (2011) DURATION-2: Efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Med 28*: 705–14

"Treatments should be tailored to individual patients, based on their specific needs, comorbidities, and adverse effects with different therapies, and cost considerations should be taken into account."