

# The role of GLP-1 receptor agonists as weight loss agents in patients with and without type 2 diabetes

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## Abstract

Obesity contributes to the pathogenesis of type 2 diabetes (T2DM) and cardiovascular disease. A modest weight loss of 5–10% can have significant impact on glucose control, medications use and patients' functionality and quality of life. Until recently, only orlistat was approved in Europe for weight loss. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown to improve glycaemia in patients with T2DM with an added benefit of weight reduction. However, the weight loss varies considerably within class and between individuals with up to 30% of patients not losing weight with GLP-1 RA treatment.

GLP-1 RAs were placed as a possible second-line treatment as an add on to metformin by the latest ADA/EASD joint guidelines while NICE placed them as third-line agents for patients with T2DM and a body mass index (BMI)  $\geq 35\text{kg/m}^2$  and inadequate glycaemic control. NICE recommended that GLP-1 RAs can be used in patients with BMI  $< 35\text{kg/m}^2$  in ethnic groups, when used as an alternative to insulin where insulin treatment has vocational implications, or if weight loss would be beneficial for other medical reasons. A GLP-1 RA (Saxenda) has recently been approved by the FDA and EMA as a weight loss treatment in patients without T2DM.

This paper aims to review the impact of GLP-1 RA treatment on weight loss in patients with and without diabetes, from clinical trials as well as real-life UK data from the ABCD nationwide audits, and also discuss the future role of GLP-1 RAs. Copyright © 2015 John Wiley & Sons.

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## Key words

GLP-1 receptor agonists; obesity; weight loss; type 2 diabetes mellitus

## Introduction

Obesity contributes to the pathogenesis of type 2 diabetes (T2DM) and cardiovascular disease. The risk of developing T2DM is seven-fold with obesity, and three-fold for overweight people compared to a healthy weight.<sup>1</sup> The increasing prevalence of T2DM is mirrored by the increasing prevalence of overweight/obesity, with data from England showing that 62% of adults in 2012 were either overweight or obese, with one person in four being obese.<sup>2</sup>

Diet and lifestyle remain the mainstay of treatment for obesity,<sup>3,4</sup> but achieving significant sustained long-term weight loss is difficult in real life. In addition, there is the lack of effective medical treatments that result in long-term weight loss. As a result, bariatric surgery, although not risk-free, is increasingly performed to achieve sustained significant weight loss with significant impact on T2DM, cardiovascular disease and mortality. Orlistat is currently the only drug in use to treat obesity in the European Union, but its use is

limited due to its gastrointestinal (GI) side effects and relatively modest weight loss. Rimonabant and sibutramine, though effective, have been withdrawn due to serious psychological and cardiovascular side effects. The US Food and Drug Administration (FDA) approved the use of Belviq (lorcaserin) and Qsymia (phentermine/topiramate) in 2012, but this is not approved in the European Union. More recently, Saxenda (liraglutide 3.0mg) has been approved for use by the FDA and the European Medicines Agency (EMA) for the treatment of obesity.

The incretin effect was first described by Elrick *et al.*, following the observation that insulin responses to oral glucose exceed those measured after IV administration of equivalent amounts of glucose.<sup>5</sup> The incretin effect in healthy individuals is responsible for 50–70% of the insulin response to a meal.<sup>6</sup> GLP-1 response in patients with T2DM is reduced, which made GLP-1 RAs an attractive therapeutic option. In addition to their impact on the

beta cell, GLP-1 RAs inhibit glucagon secretion from alpha cells and have extra-pancreatic effects such as slowing of gastric emptying and increased satiety; all of which contribute to improved glycaemia and weight loss.<sup>7</sup>

It has been shown that modest sustained weight loss reduces the incidence of T2DM,<sup>3,8,9</sup> and that 5–10% weight loss improves glycaemic control.<sup>10</sup> Traditional glucose-lowering agents, such as sulphonylureas, glitazones and insulin, improve glycaemic control but cause weight gain, whereas newer treatments such as GLP-1 RAs and sodium glucose transporter-2 (SGLT-2) inhibitors result in weight loss. Current NICE guidelines recommend the use of GLP-1 RAs in T2DM as third-line agents with inadequate blood glucose control (HbA<sub>1c</sub>  $\geq$  7.5%, 59mmol/mol) and BMI  $\geq$  35kg/m<sup>2</sup> (with appropriate adjustment for ethnicity). They are also recommended in lower BMIs where the use of insulin would cause significant implications for occupation or if weight loss would benefit other significant obesity-related comorbidities. The recommendation is that treatment should be stopped if 3% weight loss and HbA<sub>1c</sub> reduction of 1% (11mmol/mol) are not achieved after six months of treatment.<sup>11</sup>

Currently available GLP-1 RAs include: exenatide twice daily (exenatide BID); liraglutide (Victoza) once daily; and exenatide QW (Bydureon) once weekly; and, more recently, lixisenatide (Lyxumia) once daily (EMA only, FDA currently under review), dulaglutide (Trulicity) once weekly, and albiglutide (Tanzeum or Eperzan) once weekly. Currently, all the above-mentioned GLP-1 RAs are approved by the EMA for use in combination with any other oral glucose-lowering agents (except DPP-4 inhibitors and SGLT-2 inhibitors) and basal insulin except exenatide QW which is not licensed to be used with basal insulin. Dulaglutide and albiglutide are also licensed as monotherapy in patients who are intolerant to metformin.

In this review, we aimed to assess the impact of GLP-1 RA treatment on weight loss in patients with and without T2DM, with a particular focus on randomised controlled trials as well as the Association of British Clinical Diabetologists (ABCD) audits.

### Impact of GLP-1 RAs on weight loss in patients with T2DM

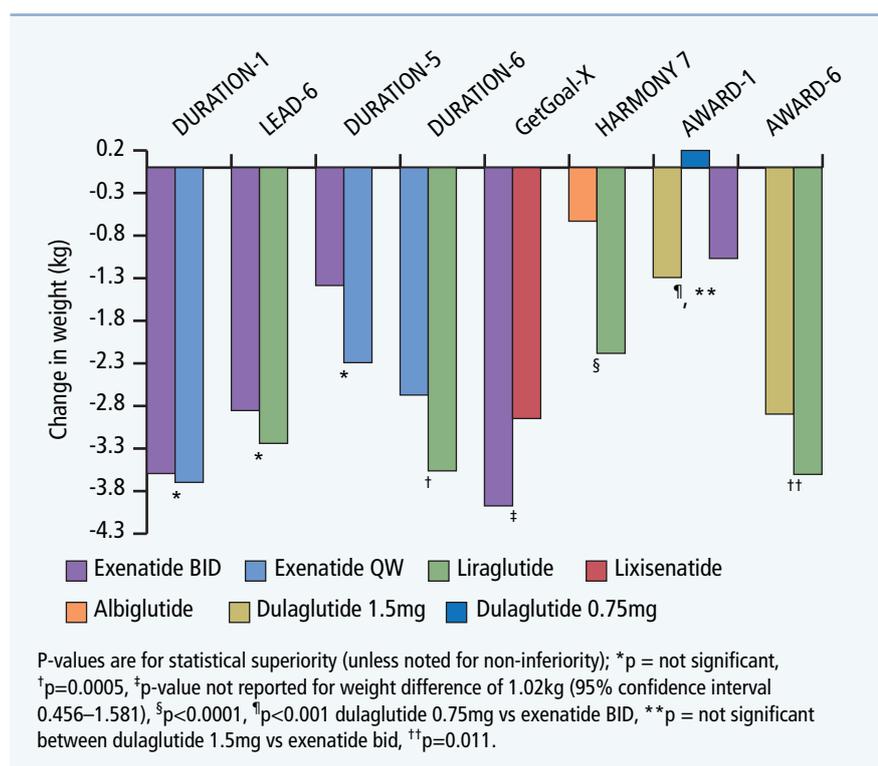
**GLP-1 RAs as monotherapy or as add on to oral medications.** In the pooled analysis of data from the AMIGO trials, exenatide BID resulted in a mean weight loss of 4.0–4.4kg after 82 weeks even when added to a sulphonylurea.<sup>12,13</sup> The impact of exenatide on weight loss was sustained at three years (-5.3kg).<sup>14</sup> In the LEAD trials, liraglutide treatment resulted in 1–3.2kg weight loss over 26–52 weeks, when used as monotherapy or as add on to metformin or metformin + rosiglitazone, with no weight gain when added to glimepiride.<sup>15–18</sup> The weight loss observed with liraglutide was dose-dependent.<sup>19</sup> In the DURATION-2 trial, exenatide QW 2mg resulted in significantly greater weight loss over 26 weeks (-2.3kg; 95% CI -2.9 to -1.7) compared to 100mg sitagliptin (-0.8kg; -1.4 to -0.1;  $p=0.0002$ ) or 45mg pioglitazone (2.8kg; 2.2 to 3.4;  $p<0.0001$ ).<sup>20</sup> The GetGoal studies for lixisenatide showed no significant weight loss compared to placebo when used as monotherapy (Get Goal-Mono), or as add on to metformin (GetGoal-M) or pioglitazone (GetGoal-P).<sup>21–23</sup> However, lixisenatide resulted in a modest but significant weight loss compared to placebo when added to a sulphonylurea in the GetGoal-S study (-1.76 $\pm$ 0.2kg vs -0.93 $\pm$ 0.23kg;  $p<0.0001$ ).<sup>24</sup> Dulaglutide (0.75–1.5mg weekly) resulted in 1.4–3.0kg weight loss when used as monotherapy or as add on to metformin (AWARD-3).<sup>25</sup> The weight reduction of dulaglutide 1.5mg weekly was similar to metformin when used as monotherapy and was greater than sitagliptin when used as add on to metformin (AWARD-5).<sup>26</sup> When used as an add on to metformin only, glimepiride with metformin, or pioglitazone (with or without metformin), albiglutide 30mg was weight neutral and comparable to placebo over 52–104 weeks (HARMONY 1, 3 and 5).<sup>27–29</sup> However, while albiglutide was weight neutral, the combination of pioglitazone + glimepiride + metformin or glimepiride + metformin resulted in weight gain (HARMONY 3 and 5).<sup>28,29</sup>

**GLP-1 RAs as add on to insulin or compared to insulin.** When compared to insulin glargine or biphasic

insulin aspart, exenatide BID resulted in modest but significant weight loss compared to weight gain with insulin (between group difference: -2.2 to -5.4kg).<sup>30–33</sup> When added to insulin, adjunctive exenatide BID was associated with statistically significant greater weight loss or mitigation of weight gain compared with placebo.<sup>34</sup>

When added to metformin and sulphonylurea, liraglutide resulted in greater weight loss compared to glargine over 26 weeks (LEAD-5); (treatment difference: -3.43kg; 95% CI 4.00, 2.86;  $p<0.0001$ ).<sup>35</sup> The addition of insulin detemir to liraglutide 1.8mg + metformin treatment did not result in weight gain over 52 weeks in patients who already lost 3.5kg on liraglutide 1.8mg + metformin prior to receiving detemir.<sup>36</sup> Fixed-ratio combination of insulin degludec and liraglutide (IDegLira) over 52 weeks was weight neutral compared to weight gain with degludec alone (treatment difference: -2.8kg;  $p<0.0001$ ), or weight loss with liraglutide alone (treatment difference: 2.66kg;  $p<0.0001$ ).<sup>37</sup> When added to degludec, liraglutide resulted in modest but significant weight loss compared to modest weight gain when once-daily insulin aspart was added to degludec (treatment difference: -3.75kg; 95% CI -4.70, -2.79;  $p<0.0001$ ).<sup>38</sup>

In the DURATION-3 trial, exenatide QW was associated with significantly greater weight loss (-2.49 $\pm$ 0.28kg) compared to glargine (2.0 $\pm$ 0.28kg;  $p<0.001$ ) over three years.<sup>39</sup> Lixisenatide resulted in modest weight loss compared to placebo when added on to a basal insulin in the GetGoal-L study (-1.8 $\pm$ 0.2kg vs -0.5 $\pm$ 0.3kg;  $p<0.0001$ ).<sup>40</sup> When added to glargine, lixisenatide resulted in 0.9kg weight loss compared to placebo.<sup>41</sup> In the AWARD-4 trial, dulaglutide 1.5mg resulted in weight loss (-0.87kg) while dulaglutide 0.75mg was weight neutral at 26 weeks, compared to significant weight gain with glargine (+2.33kg).<sup>42</sup> Albiglutide resulted in weight loss while there was weight gain with glargine over 52 weeks in HARMONY 4 (-1.06 $\pm$ 3.80kg vs +1.57 $\pm$ 3.81kg;  $p<0.0001$ ) and insulin lispro over 26 weeks in HARMONY 6 (-0.7 $\pm$ 0.2kg vs +0.8 $\pm$ 0.2kg;  $p<0.0001$ ).<sup>43,44</sup>



**Figure 1.** Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.<sup>48</sup> (Figure reproduced from *The Adv Endocrinol Metab* 2015;6[1]:19–28)

### Impact of GLP-1 RAs on weight loss in patients without T2DM

Exenatide BID resulted in greater weight loss compared to placebo ( $-5.1 \pm 0.5$  vs  $-1.6 \pm 0.5$  kg;  $p < 0.001$ ) over 24 weeks in obese patients without T2DM.<sup>45</sup> In women with polycystic ovarian syndrome but without T2DM, exenatide BID resulted in greater weight loss over 24 weeks than metformin ( $-6.0 \pm 0.5$  kg,  $-3.2 \pm 0.1$  kg and  $-1.6 \pm 0.2$  kg for exenatide + metformin vs exenatide vs metformin, respectively;  $p < 0.003$ ).<sup>46</sup>

Liraglutide 3.0 mg (Saxenda) has been approved by the FDA and more recently by the EMA for use in overweight/obese patients without T2DM. The SCALE trial randomised 3600 subjects with a BMI  $> 30$  or  $> 27$  kg/m<sup>2</sup> with comorbidities to liraglutide 3.0 mg vs placebo on the background of lifestyle intervention for 56 weeks. The dropout rate was high in both groups (28% and 36%). Liraglutide resulted in greater weight loss than placebo ( $8.4 \pm 7.3$  kg vs  $2.8 \pm 6.5$  kg;  $p < 0.001$ ). Approximately two-thirds lost 5% of their body weight, one-third lost 10% of their body weight and 14.4% lost 15% of their body weight with liraglutide 3.0 mg.<sup>47</sup>

### Head-to-head GLP-1 RA trials

There is limited literature comparing GLP-1 RAs head-to-head (Figure 1) in terms of weight loss.<sup>48</sup> Exenatide BID was superior to lixisenatide and non-inferior to liraglutide 1.8 mg, exenatide QW and dulaglutide 1.5 mg. On the other hand, liraglutide 1.8 mg was superior to albiglutide, exenatide QW and dulaglutide 1.5 mg.

### ABCD nationwide audits

Real-life data were collected by the ABCD in the nationwide audit of exenatide BID and liraglutide over two years, with an ongoing audit for exenatide QW. The patients started on GLP-1 RA were heavier (mean BMI around 39 kg/m<sup>2</sup>) and had a higher baseline HbA<sub>1c</sub> (mean 9.4%) than the reported clinical trials, and had a significant improvement in HbA<sub>1c</sub> of around 0.75% for exenatide BID and 1% for liraglutide at three and six months.<sup>49,50</sup> There was also a significant weight reduction at three months and six months with both exenatide BID ( $-4.4$  kg and  $-6.5$  kg, respectively) and liraglutide ( $-3.0$  kg and  $-3.5$  kg, respectively). Around 40% of those in the exenatide audit were also on insulin

which at the time of the audit was off licence. Although the improvement in HbA<sub>1c</sub> for those on insulin was less than that for those not on insulin, most of the patients were able to reduce or stop their insulin and sulphonylureas.<sup>51</sup> The audit highlighted that the NICE recommendations of 3% body weight reduction and 1% drop in HbA<sub>1c</sub> at six months were too restrictive as some patients responded with either weight loss or reduction in HbA<sub>1c</sub>, and only 25–29% met the NICE criteria for both weight and HbA<sub>1c</sub> at six months.<sup>51</sup>

### Discussion

GLP-1 RAs are effective in improving glycaemia with low risk of hypoglycaemia compared to sulphonylureas and/or insulin. Although overall GLP-1 RA treatment is associated with weight loss, there seems to be a large degree of inter-individual variability in the extent of weight loss achieved, with 15–30% of patients actually gaining weight.<sup>19</sup> Predictors of weight loss in GLP-1 RAs are poorly identified, but higher baseline weight and longer duration of GI side effects seem to predict weight loss in GLP-1 RA treated patients.<sup>19</sup> As noted in the ABCD audits, patients with a higher baseline weight seemed to lose more weight but had less benefit in terms of glycaemic control.<sup>51</sup> Therefore, the guidance of using GLP-1 RAs in only those with a BMI  $> 35$  may deprive some patients who could have a greater benefit in terms of glycaemic control.

In addition, the weight loss seems to vary considerably between individual GLP-1 RAs with a degree of dose dependence, particularly for liraglutide and dulaglutide. However, GI side effects and cost might limit the use of higher doses. Recent data that weight loss with exenatide QW was maintained at  $-3.0$  kg (95% CI  $-4.6$  to  $-1.3$  kg) even at five years support the durability of action of GLP-1 RA therapy over time.<sup>52</sup>

Comparison of data from different clinical trials needs to be done with caution, given the heterogeneous populations and the different treatment combinations used, although liraglutide 1.8 mg seems to result in greater weight loss

compared to most other GLP-1 RAs (except exenatide BID). Nonetheless, NICE does not currently recommend liraglutide 1.8mg daily based on the cost–benefit analysis compared to 1.2mg. However, there is no head-to-head evidence to support the superiority of the NICE recommended dose of liraglutide 1.2mg daily. Systematic reviews and meta-analysis of GLP-1 RAs that have included data from trials of liraglutide 1.2mg daily and 1.8mg daily, as well as exenatide BID and exenatide 2mg QW, have demonstrated that GLP-1 RAs as a class result in weight loss, but have failed to show a difference between these agents in different doses.<sup>53,54</sup> However, in the head-to-head trials, albiglutide and lixisenatide seem to have less weight loss effect than other GLP-1 RAs (Figure 1).

The use of GLP-1 RA as a weight loss agent in patients without T2DM is interesting and the results of the SCALE study are impressive. However, in the SCALE study, patients with severe depression and psychiatric disorders (which compromise a significant proportion of patients attending weight management clinics) were excluded. Additionally, the impact of Saxenda was less impressive in patients with a BMI of >40kg/m<sup>2</sup>, which again comprises a large proportion of patients seen in weight management/ bariatric clinics in the UK. Saxenda was also associated with a greater incidence of nausea, vomiting, gall bladder disease, pancreatitis, breast cancer and suicide compared to placebo.<sup>47</sup> While not all of these were statistically significant, safety remains a concern, particularly given that patients may use the medication long term. Saxenda is currently marketed for a significant cost in the US and, while we do not know the cost in the UK, it is unlikely that Saxenda will be cheap. However, the cost–benefit analysis will need to take into account the high cost of obesity and its complications.

GLP-1 RAs are not licensed for use with SGLT-2 inhibitors, although it is plausible that combination therapy can be beneficial as both classes have complementary mechanisms of action and both have low risk of hypoglycaemia and possibly additive

### Key points

- GLP-1 receptor agonists (GLP-1 RAs) result in mean weight loss ranging from 0.4kg to 5.1kg, although there seems to be considerable difference within the class
- There is a limited number of head-to-head trials comparing various GLP-1 RAs. There is a need for more head-to-head clinical trials, particularly comparing liraglutide 1.2mg with other GLP-1 RAs, as current trials have compared liraglutide 1.8mg which is not recommended by NICE
- In the SCALE trial, higher-dose liraglutide 3.0mg resulted in a mean weight loss of 8.4kg (8% body weight) at 56 weeks, compared to 2.8kg (2.6% body weight) with placebo. However, the treatment was associated with significant side effects, and the cost effectiveness would need to be established

weight loss effect. Some small observational studies also support this notion.<sup>55</sup> Similarly, combining GLP-1 RAs with a pre-mixed or basal-bolus insulin regimen is unlicensed but in use as shown in the ABCD audit.<sup>56</sup>

### The future of GLP-1 RAs

One of the drawbacks of GLP-1 RA therapy has been that it is an injection. Although once-weekly injections are now available compared to the previous twice-daily or once-daily preparations, future possibilities include an oral preparation of a new GLP-1 RA, semaglutide, which has shown results comparable to the injectable form in Phase 2 trials, with weight loss of 6.5kg at 26 weeks.<sup>57</sup> Continuous delivery of up to 80µg/day of exenatide via an SC miniature osmotic pump is another future treatment possibility with Phase 2 trials suggesting weight loss of -2.4 to -4.2kg at 48 weeks.<sup>58</sup> Another area for future drug development may be in combination peptides for an additive or synergistic effect. These may include combining GLP-1 with glucagon, gastric inhibitory polypeptide, gastrin, islet amyloid polypeptide and leptin.<sup>59</sup>

GLP-1 RAs are now widely used in the treatment of T2DM and more recently to treat obesity. As GLP-1 RAs inhibit glucagon and slow gastric emptying in addition to the incretin effect, several studies assessing the impact of GLP-1 RAs in patients with type 1 diabetes are ongoing. Most of the side effects of GLP-1 RAs are GI-related (nausea in particular). However, there remain some concerns about long-term safety, particularly with regard to the possible risk of pancreatitis and/or pancreatic cancer.<sup>60</sup> There are also

some concerns due to the increase in heart rate of 2–3 beats/min seen with liraglutide and exenatide.<sup>61,62</sup> Several trials assessing the cardiovascular safety of GLP-1 RAs are ongoing, with results from the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial showing no increase in cardiovascular risk nor increase in heart rate with lixisenatide. The use of GLP-1 RAs off licence is common, but further studies need to address this gap. Although, Saxenda is approved for the treatment of obesity regardless of T2DM, its place in the treatment algorithm in real life and its cost effectiveness remain to be determined.

### Declaration of interests

SD has no conflicts of interest to declare.

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