

# Adjunct liraglutide use in people with type 1 diabetes in the St Vincent's Healthcare Group, Dublin: An Irish perspective

Patricia Harkin, Malachi McKenna, Ronan Canavan,  
Rachel Crowley, Donal O'Shea

**Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved for use in the management of hyperglycaemia in type 2 diabetes since 2009. In clinical trials, these agents have been shown to improve glycaemic control, aid weight loss and improve cardiovascular and renal outcomes. They have also been used off label as adjunct therapies in people with type 1 diabetes to stabilise glycaemic control, reduce weight and reduce daily insulin doses. The aim of this audit was to report the real-world experience of using the GLP-1 RA liraglutide in people with type 1 diabetes within the St Vincent's Healthcare Group, Dublin. Twelve people with up to 48 months' exposure to liraglutide were evaluated. The results revealed this agent was well tolerated and, in certain patients, had a positive impact on weight, glycaemic control and total daily insulin dose.**

Since 2009, new therapies have joined the treatment algorithm for the management of hyperglycaemia in type 2 diabetes. These include glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors. The American Diabetes Association and European Association for the study of Diabetes consensus guideline recommends that, in people with type 2 diabetes and established atherosclerotic cardiovascular disease, treatment for hyperglycaemia should be diet, lifestyle change and metformin, followed by, if this does not achieve target HbA<sub>1c</sub> levels, an agent proven to reduce cardiovascular mortality risk (Davies, 2018). To date, the latter includes the GLP-1 RAs liraglutide and semaglutide, and the SGLT2 inhibitors empagliflozin and canagliflozin.

## GLP-1 RAs

There are currently four GLP-1 RAs available in

Ireland: exenatide, liraglutide, dulaglutide and the recently launched semaglutide. All diabetes medications are covered under the Long Term Illness Scheme with the Health Service Executive (HSE) Ireland. At present, the HSE reimburses liraglutide up to the dose of 1.8 mg.

GLP-1 RAs assist glucose homeostasis through several mechanisms (*Figure 1*). Satiety is primarily achieved via a delay in gastric emptying and absorption of carbohydrate from the gastrointestinal tract. The agents promote insulin secretion by the pancreatic islet cells and inhibit gluconeogenesis by the liver. There is also the added benefit of not inducing hypoglycaemia.

GLP-1 RAs are contraindicated in people with a history of pancreatitis or thyroid medullary carcinoma. They can be used in patients with an estimated glomerular filtration rate over 15 mL/min/1.73 m<sup>2</sup>.

This article focuses on the GLP-1 RA liraglutide and presents an Irish audit highlighting its use in people with type 1 diabetes.

**Citation:** Harkin P, McKenna M, Canavan R, Crowley R, O'Shea D (2019) Adjunct liraglutide use in people with type 1 diabetes in the St Vincent's Healthcare Group, Dublin: An Irish perspective. *Journal of Diabetes Nursing* 23: JDN061

## Article points

1. Adjunct therapies are being used off label to stabilise glucose control, reduce weight and reduce total daily dose of insulin in people with type 1 diabetes.
2. This retrospective Irish audit was conducted to establish real-world experience of adjunct liraglutide use in 12 patients with type 1 diabetes.
3. Discretionary use of liraglutide in select cases may confer benefit in patients with type 1 diabetes who are overweight.

## Key words

- Glucagon-like peptide-1 receptor agonists
- Newer therapies
- Type 1 diabetes
- Weight loss

## Authors

Author details can be found on page 5.

**Page points**

1. In clinical trials, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown benefits in terms of glycaemic control, weight loss and cardiovascular and renal outcomes in people with type 2 diabetes.
2. Ongoing research also suggests that GLP-1 RA therapy, as an adjunct to insulin, can assist people with type 1 diabetes with weight loss and reducing daily insulin dose.
3. The most common side effects in the latter patient group are hypoglycaemia and ketosis.

**Studies of GLP-1 RAs in type 2 diabetes**

GLP-1 RAs have shown effects on glycaemic control and weight loss in clinical trials. A Cochrane systematic review of GLP-1 RAs in people with type 2 diabetes revealed HbA<sub>1c</sub> reductions of approximately 11 mmol/mol (1.0%) and weight reductions of 1.5–2.5 kg compared with baseline (Shyangdan et al, 2011). This weight loss was further confirmed in another meta-analysis of 21 trials (Vilsbøll et al, 2012).

Two GLP-1 RAs have shown cardiovascular benefits in cardiovascular outcome trials. Compared with placebo, liraglutide significantly reduced the risk of major adverse cardiovascular events (MACE) by 13%, including a 22% risk reduction in cardiovascular death, a 12% reduction in non-fatal myocardial infarction (MI) and an 11% reduction in non-fatal stroke (Marso et al, 2016a). There was also benefit in terms of renal outcomes. Similarly, semaglutide resulted in a 26% reduction in MACE risk compared with placebo, including a 26% reduction in non-fatal MI and a 39% reduction in non-fatal stroke (Marso et al, 2016b).

Despite similar mechanisms of action, the agents within the GLP-1 RA class differ in their clinical effects due to differences in structures and pharmacokinetic profiles (Pratley et al, 2018). Liraglutide has resulted in greater HbA<sub>1c</sub> and weight

reductions in comparison with the other GLP-1 RAs in three clinical trials (Buse et al, 2009; Buse et al, 2013; Dungan et al, 2014). Liraglutide has also shown superiority to other classes of oral agents – DPP-4 inhibitors and SGLT2 inhibitors – in some studies (Pratley et al, 2010; Pratley et al, 2011; Lorenzi et al, 2017).

**Efficacy and safety of liraglutide in type 1 diabetes**

Incretin-based therapies (GLP-1 RAs and DPP-4 inhibitors) have the potential to protect beta-cell mass, trigger insulin release and suppress glucagon release (Nauck et al, 2009). Two key studies have examined the efficacy and safety of liraglutide in type 1 diabetes. ADJUNCT ONE was a 52-week, double-blind, treat-to-target study conducted in 1398 people randomised 3:1 to receive liraglutide (1.8 mg, 1.2 mg or 0.6 mg) or placebo, in 177 centres in 17 countries (Mathieu et al, 2016). The results showed weight loss of 4.9 kg, 3.6 kg and 2.2 kg, respectively, compared with placebo, and small improvements in HbA<sub>1c</sub>. Insulin total daily dose (TDD) was also reduced by 5% and 2% with liraglutide 1.8 mg and 1.2 mg; however, it increased by 4% with the 0.6 mg dose. The main complications were increased risk of symptomatic hypoglycaemia with all doses, and hyperglycaemia

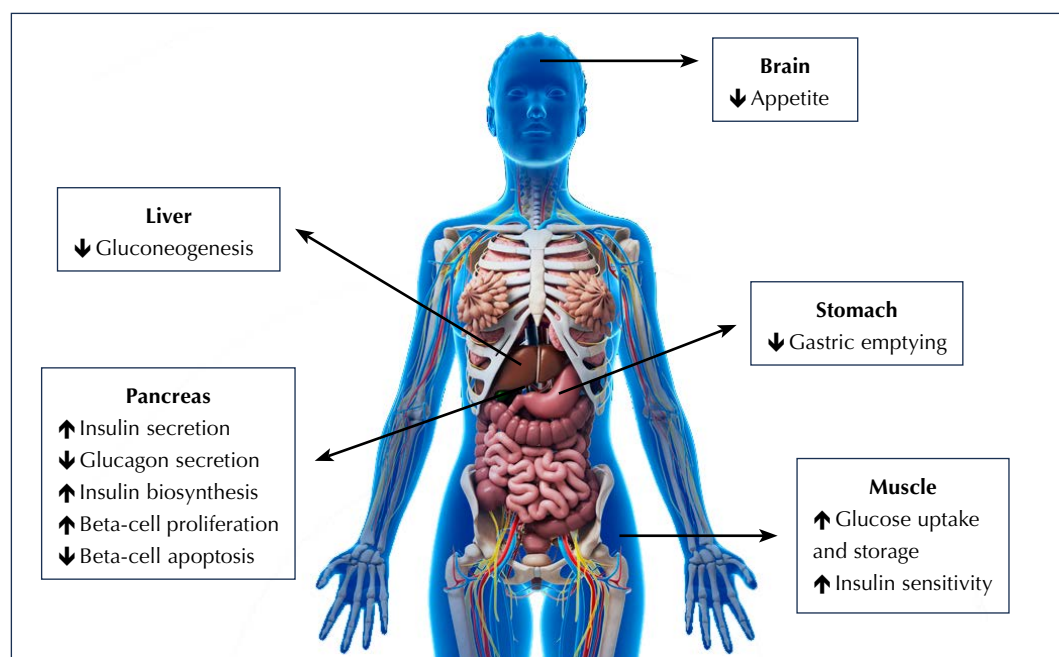


Figure 1. Mechanisms through which glucagon-like peptide-1 receptor agonists reduce blood glucose levels.

with ketosis for the 1.8 mg dose only.

ADJUNCT TWO was a 26-week, double-blind, parallel-group trial with 835 people randomised 3:1 to liraglutide or placebo (Ahrén et al, 2016). Outcomes revealed significant reductions in HbA<sub>1c</sub>, weight and TDD, and improved quality of life. Again, the complications were hypoglycaemia and, with the 1.8 mg dose, ketosis. The authors stated that these side effects limited the clinical use of GLP-1 RAs in people with type 1 diabetes.

### Dublin audit

While they are not currently approved by the US Food and Drug Administration for this indication, St Vincent's Healthcare Group in Dublin uses GLP-1 RAs off label as adjunct therapies in select patients with type 1 diabetes to stabilise glucose control, reduce weight and reduce insulin TDD. The aim of this retrospective audit was to establish real-world effects of liraglutide use in people with type 1 diabetes.

There are currently 8783 active patients listed on our dedicated diabetes database between the three hospitals in St Vincent's Healthcare Group: 5677 in St Vincent's University Hospital, 1692 in St Michael's Hospital and 1414 in St Vincent's Private Hospital. The audit commenced in March 2018 and finished in April 2018. The database revealed 554 people on liraglutide. Those with type 2 diabetes and two brothers with monogenic diabetes were excluded. Twelve people with type 1 diabetes were identified and evaluated.

Liraglutide was initiated at the dose of 0.6 mg once daily and titrated up to 1.2 mg or 1.8 mg according to tolerance. One patient moved to a 2.4 mg dose temporarily. Liraglutide is licensed up to 3.0 mg to treat obesity; however, as stated previously, the HSE in Ireland only reimburses up to 1.8 mg in people with diabetes.

### Results

The individual characteristics and clinical outcomes of the 12 participants are shown in *Table 1*. Over a mean treatment duration of 22 months (range, 1–48 months), eight participants lost weight, with an average loss of 6.7 kg. Two people increased their weight (by 6.7 kg and 3.5 kg, respectively) and two had no weight data at follow-up as they had not been back for clinic review. Mean BMI in those who

lost weight was reduced from 32.7 to 29.9 kg/m<sup>2</sup>.

HbA<sub>1c</sub> fell in five people, by a mean of 9.6 mmol/mol (0.9%); however, it rose by a mean of 4.4 mmol/mol (0.4%) in five and stayed the same in one. One participant had not had an HbA<sub>1c</sub> measurement at follow-up. Insulin TDD was reduced in five participants, by an average of 16.4 units.

There were no episodes of hypoglycaemia (defined as a blood glucose of <4 mmol/L) or diabetic ketoacidosis whilst on liraglutide therapy, and no emergency hospital admissions. Patients 6 and 7 have discontinued treatment as they are planning pregnancy.

### Discussion

In our practice, GLP-1 RA initiation is considered as a potential adjunct therapy in overweight and obese people with type 1 diabetes. Clinical review of patients can determine whether GLP-1 RAs may be beneficial to assist weight loss in this cohort, even if the practice is off-label. The current audit suggests that, in certain patients with type 1 diabetes, the GLP-1 RA liraglutide had modest benefits in terms of glycaemic control, weight loss and insulin dose reduction. However, a subset of patients did not respond to this therapy.

Liraglutide was well tolerated, with no episodes of hypoglycaemia or diabetic ketoacidosis. Patients were made aware of the increased risk of hypoglycaemia that occurs when GLP-1 RAs are added to insulin therapy, due to effects on gluconeogenesis and glycogen stores in the liver, and were advised to be vigilant. Insulin dose reduction was recommended, and five participants reduced their TDD by a mean of 16.4 units. A reduction in insulin TDD can assist with weight loss in patients who are overweight.

A large proportion of this cohort had completed the Dose Adjustment for Normal Eating (DAFNE) structured education programme, which has the benefit of allowing patients to find their own insulin TDD requirement. A lot of patients on inappropriate insulin doses increase their food intake to avoid hypoglycaemia, and this can lead to weight gain. The DAFNE programme assists them to identify their own individual dose requirements, and thus a proportion of DAFNE participants lose weight following the programme. In addition,

### Page points

1. The current audit, conducted in Dublin, revealed 12 people with type 1 diabetes who have received the GLP-1 RA liraglutide as an adjunct to insulin therapy.
2. Over a mean treatment duration of 22 months, eight of the 12 patients lost weight, while two gained weight.
3. HbA<sub>1c</sub> fell in five patients but increased in another five. Insulin total daily dose was reduced in five participants, by an average of 16.4 units.
4. Liraglutide was well tolerated, with no episodes of hypoglycaemia, diabetic ketoacidosis or emergency hospital admissions.

**Table 1. Participant characteristics and clinical outcomes before and after addition of liraglutide to insulin therapy.**

Participant	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	49	33	25	50	43	34	31	44	51	54	57	35
Gender	F	F	F	F	M	F	F	F	F	F	F	F
Duration of diabetes (years)	22	27	17	11	21	8	14	19	37	40	57	28
<b>Weight (kg)</b>												
Baseline	81	75.6	93.0	99.3	108.1	103.0	107.0	101.9	74.6	79.9	93.2	110.0
Follow-up	74.6	68.0	91.6	92.4	100.7	No data	113.7*	90.5	No data	73.0 <sup>†</sup>	96.7*	104.6
Weight loss (gain denoted by ↑)	6.4	7.6	1.4	6.9	7.4	n/a	↑6.7	11.4	n/a	6.9	↑3.5	5.4
<b>BMI (kg/m<sup>2</sup>)</b>												
Baseline	27.7	28.1	n/a <sup>‡</sup>	35.6	32.6	34.5	37	35.3	30.3	28.6	31.5	38.5
Follow-up	25.5	25.3	n/a <sup>‡</sup>	33.1	30.4	No data	39.3	31.3	No data	26.1	32.7	38.0
BMI reduction (gain denoted by ↑)	2.2	2.8	n/a	2.5	2.2	n/a	↑2.3	4	n/a	2.5	↑1.2	0.5
<b>HbA<sub>1c</sub> (mmol/mol)</b>												
Baseline	71	56	63	82	76	72	83	56	64	73	83	79
Follow-up	60	56	56	89	72	73	71	59	No data	68	67	81 <sup>§</sup>
HbA <sub>1c</sub> reduction (gain denoted by ↑)	11	N/A	↑8	↑8	4	↑1	12	↑3	n/a	5	16	↑2
Liraglutide dose (mg)	1.8	1.8	1.8 (max 2.4)	1.8	1.8	1.8	1.8	1.8	0.6	1.2	1.8	0.6
Liraglutide duration (months)	5	16	30	27	38	8	36	6	1	2	48	44
Insulin delivery	MDI (ex-CSII)	CSII	MDI (+ Met)	MDI	MDI (+ Met)	MDI	MDI	CSII	CSII	CSII	MDI	CSII (2 years; + Met)
DAFNE	2006, 2014	2017 (CSII)	No	No	2012	2012	2016	2008 (CSII), 2017 (MDI)	2014	No	No	2012
Emergency admission	No	No	No	No	No	No	No	No	No	No	No	No
Insulin TDD reduction (units)	23	23	No	No	Initially	No	No	16	No	10	10	No

\*Initial weight loss but net gain at follow-up. <sup>†</sup>Self-reported weight from own scales. <sup>‡</sup>Height not measured. <sup>§</sup>Initial HbA<sub>1c</sub> reduction but net increase at follow-up.

CSII=continuous subcutaneous insulin infusion; DAFNE=Dose Adjustment for Normal Eating; MDI=multiple daily injections; Met=metformin; TDD=total daily dose.

while DAFNE allows flexibility in the foods eaten, healthy eating is advocated in all participants who are not within a normal BMI.

Eight of the current cohort had completed the DAFNE programme: six had completed regular DAFNE (one had completed it twice), two had completed the insulin pump course and one had completed both regular and pump courses. DAFNE graduates did not appear to be more likely to benefit from liraglutide than non-graduates.

The sample cohort in this audit was small, which is appropriate as we are not recommending widespread initiation of GLP-1 RAs in patients with type 1 diabetes. In our practice, adjunct therapies are only maintained if they have the desired impact in terms of weight loss or reductions in HbA<sub>1c</sub>. Due to the costly nature of GLP-1 RA therapy, the decision is made to discontinue treatment in non-responders.

## Conclusion

Discretionary use of GLP-1 RAs in select cases may confer benefits in people with type 1 diabetes who are overweight. Weight gain in people with type 1 diabetes can be attributed in part to inappropriate insulin doses, as we have seen significant weight loss in graduates of the DAFNE structured education programme in post-course follow-up. ■

Ahrén B, Hirsch IB, Pieber TR et al; ADJUNCT TWO Investigators (2016) Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. *Diabetes Care* **39**: 1693–701

Buse JB, Rosenstock J, Sesti G et al; LEAD-6 Study Group (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* **374**: 39–47

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

Davies MJ, D'Alessio DA, Fradkin J et al (2018) Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **41**: 2669–701

Dungan KM, Povedano ST, Forst T et al (2014) Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* **384**: 1349–57

Lorenzi M, Ploug UJ, Langer J et al (2017) Liraglutide versus SGLT-2 inhibitors in people with type 2 diabetes: a network meta-analysis. *Diabetes Ther* **8**: 85–99

Marso SP, Daniels GH, Brown-Frandsen K et al; LEADER Trial Investigators (2016a) Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **375**: 311–22

Marso SP, Bain SC, Consoli A et al; SUSTAIN-6 Investigators (2016b) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* **375**: 1834–44

Mathieu C, Zinman B, Hemmingsson JU et al; ADJUNCT ONE Investigators (2016) Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care* **39**: 1702–10

Nauck MA, Vilsbøll T, Gallwitz B et al (2009) Incretin-based therapies: viewpoints on the way to consensus. *Diabetes Care* **32**(Suppl 2): 223–31

Pratley RE, Nauck M, Bailey T et al; 1860-LIRA-DPP-4 Study Group (2010) Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* **375**: 1447–56

Pratley R, Nauck M, Bailey T et al; 1860-LIRA-DPP-4 Study Group (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: a randomised, parallel-group, open-label trial. *Int J Clin Pract* **65**: 397–407

Pratley RE, Aroda VR, Lingvay I et al; SUSTAIN 7 investigators (2018) Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* **6**: 275–86

Shyangdan DS, Royle P, Clar C et al (2011) Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev*: CD006423

Vilsbøll T, Christensen M, Junker AE et al (2012) Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* **344**: d7771

**“Discretionary use of glucagon-like peptide-1 receptor agonists in select cases may confer benefits in people with type 1 diabetes who are overweight.”**

## Authors

Patricia Harkin is Advanced Nurse Practitioner/Registered Nurse Prescriber, St Vincent's Private Hospital, and Adjunct Lecturer, University College Dublin; Malachi McKenna is Consultant Endocrinologist, St Vincent's Healthcare Group; Ronan Canavan is Consultant Endocrinologist, St Vincent's University Hospital, St Vincent's Private Hospital and St Columcille's Hospital; Rachel Crowley is Consultant Endocrinologist, St Vincent's University Hospital and University College Dublin; Donal O'Shea is Consultant Endocrinologist, St Vincent's University Hospital, St Vincent's Private Hospital and St Columcille's Hospitals, Dublin, and HSE Clinical Lead for Obesity.