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NICE NG28 (2015)	SIGN 154 (2017)	EASD-ADA guidelines (2018)
If triple therapy with metformin and two other oral drugs is ineffective, not tolerated or contraindicated, HCPs should consider combination therapy with metformin, sulfonylurea and GLP-1 RA as below.	People with BMI ≥30 kg/m² (or ethnicity-adjusted equivalent) combined with oral glucose-lowering drugs, basal insulin or both as third- or fourth-line treatment, when adequate glycaemic control not achieved.	For people with established atherosclerotic CVD, the guidelines recommend sodium–glucose cotransporter 2 (SGLT2) inhibitors or GLP-1 RAs.
BMI ≥35 kg/m² (adjust for ethnicity) and specific psychological or other medical problems associated with obesity.	As an alternative to insulin in people for whom combinations of oral glucose-lowering drugs did not produce adequate glycaemic control.	For people with CKD with or without CVD, consider a GLP-1 RA shown to reduce CKD progression (currently liraglutide and semaglutide) when an SGLT2 inhibitor shown to reduce CKD progression is contraindicated or not preferred.
BMI <35 kg/m² when insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.	Consider a GLP-1 RA with proven cardiovascular benefit for people with type 2 diabetes and established cardiovascular disease (CVD) (currently liraglutide and semaglutide).	GLP-1 RAs preferred to insulin if greater glucose-lowering effect of an injectable medication needed; insulin recommended if extreme, symptomatic hyperglycaemia.
Only continue GLP-1 RAs if the person has had a beneficial metabolic response: reduction of ≥11 mmol/mol (1.0%) in HbA_{1c} and a weight loss of ≥3% of initial body weight in 6 months.	Continue GLP-1 RA at each stage if **either** individualised HbA_{1c} target achieved **or** HbA_{1c} falls >5.5 mmol/mol (0.5%) in 3–6 months. Discontinue GLP-1 RA if ineffective.	People unable to maintain glycaemic targets on basal insulin + oral medications can have treatment intensified with GLP-1 RAs, SGLT2 inhibitors or prandial insulin.

Table 1. Summary of the currently available GLP-1 RAs.

GLP-1 RA	Injection frequency	Main pharmacological action(s)	Glucose target
Exenatide	Twice daily	↓Gastric emptying	Prandial
Liraglutide	Once daily	↑Insulin ↓Glucagon	Prandial and fasting
Lixisenatide	Once daily	↓Gastric emptying	Prandial
Exenatide, prolonged-release	Weekly	↓Gastric emptying	Prandial and fasting
Dulaglutide	Weekly	↑Insulin ↓Glucagon	Prandial and fasting
Semaglutide	Weekly	↑Insulin ↓Glucagon	Prandial and fasting

Assessing suitability

People to consider	Prescribe with caution	Unsuitable people
● People with type 2 diabetes (T2D) and high BMI, adjusted for ethnicity ● People with T2D and significant risk of cardiovascular disease (CVD) ● People with T2D and established CVD ● People with T2D and CKD or heart failure, unsuitable for SGLT2 inhibitors	● People in whom weight loss would cause concern (e.g. frailty) ● People with a history of gallstones ● Women of child-bearing age (ensure adequate contraception; GLP-1 RAs may reduce oral contraceptive efficacy) ● People with irritable bowel syndrome or gastro-oesophageal reflux disease (GORD) ● People with renal or hepatic impairment ● Active proliferative or pre-proliferative retinopathy†	● Type 1 diabetes (T1D) ● Children ● Pregnant women ● History of, or risk factors for, pancreatitis* ● History of medullary thyroid cancer or multiple endocrine neoplasia type 2

*For example: idiopathic, gallstones, alcohol abuse, trauma and hypertriglyceridaemia.

†Non-significant increase in retinopathy with liraglutide versus placebo in LEADER (0.6 vs 0.5 events per 100 patient-years respectively; hazard ratio, 1.15); retinopathy complications occurred in 3.0% of the semaglutide group and 1.8% in the placebo group (hazard ratio, 1.76) in SUSTAIN-6.

SmPC for semaglutide and exenatide advise caution in people with background retinopathy and taking insulin therapy.

About this series

The aim of the "How to" series is to provide readers with a guide to clinical procedures and aspects of diabetes care that are covered in the clinic setting.

What is the role of the incretin hormone GLP-1?

- Increases insulin secretion and insulin sensitivity.
- Increases beta-cell mass and maintains beta-cell function.
- Increases glucose disposal.
- Delays gastric emptying.
- Reduces appetite by increasing satiety.

What are GLP-1 RAs?

- Chemical modification of GLP-1 produces drugs that bind to the GLP-1 receptor, producing the same effects as the native protein.
- Current therapies all have a similar mechanism of action.
- Effects in type 2 diabetes include reductions in HbA_{1c} and weight. Some therapies have additionally demonstrated cardiovascular benefits (liraglutide and semaglutide).
- All current GLP-1 RA therapies are injectable, but have different profiles, which affects dosing frequency (see *Table 1*).

Citation: Milne N (2019) How to use GLP-1 receptor agonist therapy safely and effectively. *Diabetes & Primary Care* **21**: **45–6**

Table 2. Tailoring the drug and device to the individual.

Device	Dosing regimen and available doses	How to initiate	Other information
Dulaglutide (Trulicity)	Once weekly 0.75 mg or 1.5 mg in a pen that delivers one of the two doses	Initial dose 0.75 mg (monotherapy) and 1.5 mg (as add-in therapy) weekly. May increase dose to 1.5 mg weekly for additional glycaemic control	One-use disposable device with hidden needle
Extended-release exenatide (Bydureon)	Once weekly 2 mg	Fixed dose 2 mg weekly	One-use disposable device with hidden needle
Lixisenatide (Lyxumia)	Once daily 10 mg or 20 mg in a pen that delivers one of the two doses	Initial dose 10 mg once daily for 2 weeks then increase to 20 mg Starter kit has both strength pens	Pen device requires attachable needle
Liraglutide (Victoza)	Once daily 1 pen delivers 3 different doses: 0.6 mg, 1.2 mg or 1.8 mg	Initial dose 0.6 mg once daily for 1 week then 1.2 mg daily Escalate to 1.8 mg if further glycaemic control required or in people with established CVD*	Pen device requires attachable needle
Semaglutide (Ozempic)	Once weekly 0.25 mg, 0.5 mg or 1 mg in a pen that delivers one of the three doses	Initial dose 0.25 mg for 4 weeks then 0.5 mg for at least 4 weeks Escalate to 1 mg if further glycaemic control required	Pen device requires attachable needle (included with pens)

*Scottish Medicines Consortium has not approved 1.8 mg on grounds of cost-effectiveness.

Top ten tips for initiation

1. Consider guidelines.
2. Review for any prescribing cautions/contraindications: Always refer to product SmPC.
3. Review other medications: **Not to be prescribed with DPP-4 inhibitor**. Doses of **sulfonylureas and/or insulin may need to be reduced** to avoid initial hypoglycaemia.
4. Consider efficacy: Longer-acting GLP-1 RAs seem to benefit fasting and post-prandial glucose control.
5. Consider dosing frequency: twice daily, daily or weekly.
6. Establish if any CVD and/or CKD are present, as some GLP-1 RA therapies have demonstrated benefit in this cohort (currently liraglutide and semaglutide).
7. Consider tolerability: Clinical studies suggest that the GLP-1 RAs have comparable adverse event profiles.
8. Consider device characteristics.
9. Consider cost effectiveness.
10. Ensure effective education for the person with T2D and their families and carers.

Top ongoing considerations for effective use of GLP-1 RAs

- Side effects: See boxes below on nausea, abdominal pain and injection site reactions.
- Compliance: Studies suggest compliance can sometimes be low.
- Contraception: Ensure adequate contraception for women of child-bearing potential. GLP-1 RAs of shorter duration and that delay gastric emptying may undermine the efficacy of oral contraception.
- Pregnancy: Any risks of using GLP-1 RAs in pregnancy are unclear. Ensure GLP-1 RAs are not used in pregnancy and, for weekly GLP-1 RAs, are stopped at least 3 months prior to conception.
- Sick-day guidance: GLP-1 RAs may be associated with acute kidney injury in persons with severe gastrointestinal symptoms and dehydration. Consider stopping if at risk of dehydration until well again.
- Intensification: As per product SmPC.
- Monitoring and achieving targets: NICE recommends measuring HbA_{1c} in adults with type 2 diabetes every:
  - 3–6 months (tailored to each patient), until HbA_{1c} is stable on unchanging therapy
  - 6 months once HbA_{1c} and therapy are stable.

Nausea

- Gastrointestinal adverse events are usually mild or moderate, dose-dependent, decline with continued treatment and do not affect glycaemic control.
- Exclude any other gastrointestinal pathology.
- If the patient is unwell, check for ketones and review diagnosis.
- Reduce meal size, eat more often, reduce fat content (which slows gastric emptying).
- "Flex-pen" devices can dial up in number of "clicks" and thus more gradually increase dose until therapeutic dose is reached.
- Short-term antiemetic.
- Once-weekly treatment.

Abdominal pain

- Unusual, and likely to be associated with an underlying cause rather than being a side effect of GLP-1 RAs.

Until the relationship between GLP-1 RAs and pancreatitis is resolved: Avoid prescribing to people with risk factors for pancreatitis, such as severe hypertriglyceridaemia or excessive alcohol use, or persons with diagnosed pancreatitis.

Underlying cause	Comments
Dyspepsia	• Due to delayed gastric emptying • Consider short-term use of dyspeptic agents
Constipation	• Consider osmotic laxatives if due to delayed gastric emptying • Encourage fluids if due to reduced oral intake
Pancreatitis	• Consider especially if the patient is unwell or has a history of gallstones, elevated triglycerides or alcohol abuse • Consider hospital admission • Stop GLP-1 RA, check amylase levels and monitor closely

Injection site reactions

- Check injection technique.
- Change frequency of needle replacement.
- Evaluate patients for underlying dermatological disease.
- Consider a change in preparation as some patients react to the excipient, rather than the active GLP-1 RA.

Essential education

- Discussion of mode of action to include anticipated benefits.
- Discuss potential side effects:
  - Postprandial fullness and nausea (suggest the person eats smaller meals more frequently and stops when they start to feel full)
  - Possible worsening of GORD
  - Stop taking and seek medical advice if any sudden onset of abdominal pain
- Demonstrate the range of devices to ensure person choice.
- Assess the person's understanding and ability to use the agreed device.
- Discuss injection sites and the importance of rotating the site.
- Stress the importance of needle safety including disposal.
- Arrange appropriate monitoring and review.
  - Advise about titration (if appropriate).
  - Discuss blood glucose monitoring (especially if used with gliclazide or insulin).
  - Suggest targets for continuation of treatment.