Case study*

Managing type 2 diabetes in a person who has experienced hypoglycaemia on glucose-lowering therapy

Overview Click any of the options below to go to that section:

***Fictitious case, created for illustrative purposes only by a healthcare professional**

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Prescribing information and adverse event reporting information can be found at the end of the case study.
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Presentation details

- GN* is a 55-year-old teaching assistant who drives to work
- 4 years ago, she presented to her GP with tiredness, thirst, polyuria and a history of recurrent episodes of thrush
  - She was diagnosed with type 2 diabetes
  - At this time, her HbA_{1c} was 87 mmol/mol (10.1%) and her weight was 82 kg
- Her GP commenced her on metformin 500 mg once daily [o.d.], and as she had symptoms of hyperglycaemia[1], a sulphonylurea (gliclazide 80 mg once daily [o.d.], taken with main meal) was also prescribed[2]
  - This regimen rapidly improved her symptoms and over the following year her HbA_{1c} fell to 55 mmol/mol (7.2%)
  - However 1 year ago, GN's HbA_{1c} level began to climb
  - Her metformin dose was increased to the maximum dose she tolerated: 850 mg twice daily (b.d.); and the gliclazide dose to 80 mg twice daily (b.d.), taken with main meals
  - Her GP suggests increasing the dose of gliclazide further, but GN is concerned that since starting this medication, she had gained 3 kg in weight[3]

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Go to **Initial assessment (i)**

Initial assessment (i)

- At her last clinic visit, GN's results were as follows:

- Her current medication regimen is:

HbA_{1c}	58 mmol/mol (7.5%)
Estimated glomerular filtration rate (eGFR)	63 mL/min/1.73 m^2 (stable since time of T2D diagnosis)
Body mass index (BMI)	28 kg/m^2
Gliclazide (glucose-lowering medication for T2D)	80 mg b.d. (taken with main meals)
Metformin (glucose-lowering medication for T2D)	850 mg b.d.
Atorvastatin (for primary prevention of a cardiovascular [CV] event based on her CV disease risk)	20 mg o.d.
Lisinopril (she has a history of hypertension)	20 mg o.d.

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Go to **Initial assessment (ii)**

b.d., twice daily; o.d., once daily;
T2D, type 2 diabetes

Initial assessment (ii)

- GN is taking gliclazide and drives regularly
  - She has been supplied with a meter and strips for self-monitoring of blood glucose (SMBG) as she is at risk of hypoglycaemia when driving[2]
- Her GP is concerned about the number of testing strips GN is requesting for her SMBG, and asks her to attend a review in the diabetes clinic
  - GN mentions that at work she feels very hungry mid-morning, so has coffee and biscuits in the staffroom
  - She has also felt 'jittery' on two occasions whilst driving, and keeps a supply of mini chocolate bars in the glove compartment 'just in case'
  - She has concerns about her weight and her low blood sugar episodes and asks whether alternative treatment options are possible

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Go to **Considerations for management (i)**

Considerations for management (i)

- When considering diabetes medication, there are a number of factors for the prescriber to consider[4-10]

Age[5] | Sex[6] | Faith[7] | BMI[5] | Occupation[8]

Dexterity[9] | Driving[8] | Comorbidities[4] | Polypharmacy[10]

- In addition, the prescriber needs to be aware of renal function, hepatic function and cardiac status[4]
- Awareness of the limitations or benefits of each therapy is therefore essential when individualising therapy to the needs of a person with T2D[2,4]

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Go to **Considerations for management (ii)**

BMI, body mass index; T2D, type 2 diabetes

Considerations for management (ii)

- GN has a mild reduction in her eGFR[11] and is overweight[12]. Her options were considered as follows:
  - A dipeptidyl peptidase 4 (DPP-4) inhibitor:
    - Impedes the enzyme DPP-4, which is involved in the inactivation of the incretin hormones GLP-1 and GIP that play important roles in the physiological regulation of glucose homeostasis[13]
    - Low risk of hypoglycaemia when used with metformin[4]
    - Weight neutral[4]
    - No dose adjustment needed if GN's eGFR remains >50 mL/min/1.73min^2 [14–18] (always consult the relevant summary of product characteristics for specific information when prescribing)
      - Trajenta® (linagliptin) can be used at all stages of renal impairment with no dose adjustment needed[14]

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Go to **Considerations for management (iii)**

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide

Considerations for management (iii)

- Thiazolidinedione:
  - Reduces insulin resistance and improves insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPARγ) and promoting differentiation of fat cells[13]
  - Low risk of hypoglycaemia[4]
  - May cause fluid retention, which may exacerbate or precipitate heart failure[19]
    - GN is at higher risk of heart failure due to her type 2 diabetes and history of hypertension[20]
- A sodium–glucose co-transporter 2 (SGLT2) inhibitor:
  - Improves glycaemic control by reducing renal glucose absorption, leading to excretion of excess glucose in the urine. In addition, they increase the excretion of sodium, resulting in osmotic diuresis and reduced intravascular volume[13]
  - Low risk of hypoglycaemia when used with metformin[4]
  - Can provide some weight loss[4]
    Note: SGLT2 inhibitors are not licensed for weight loss
  - Associated with their glucosuric effect, SGLT2 inhibitors increase the risk of genital mycotic infections, particularly in women[13]

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Go to **Considerations for management (iv)**

eGFR, estimated glomerular filtration rate

Considerations for management (iv)

- A glucagon-like peptide 1 (GLP-1) receptor agonist:
  - Activates GLP-1 receptor, mimics action of GLP-1 to enhance prandial insulin secretion, reduces prandial glucagon secretion, delays gastric emptying and exerts satiety effect[13]
  - Low risk of hypoglycaemia when used with metformin[4]
  - Can provide some weight loss[4]
    Note: GLP-1 receptor agonists are not licensed for weight loss
  - NICE does not recommend use of GLP-1 receptor agonists as a second-line blood-glucose lowering option[2]
- Insulin
  - Used as a direct substitute for the body's own insulin. It is available in three injectable forms – animal, human and analogue – with a range of rates of action[21]
  - Risk of hypoglycaemia and weight gain[4]
  - NICE does not recommend use of insulin as a second-line blood-glucose lowering option[2]

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Go to **Considerations for management (v)**

Considerations for management (v)

- Having considered the options, GN asked to be switched to a dipeptidyl peptidase-4 (DPP4) inhibitor
  - She was commenced on linagliptin 5 mg once daily and the gliclazide was withdrawn, she continued to take metformin 850 mg b.d.
- GN was reminded of the importance of adhering to diet and lifestyle as part of her diabetes management plan[2] and counselled on potential side effects for her new therapy regimen
  - This included how to recognise symptoms of pancreatitis should this occur while taking a DPP-4 inhibitor[4]

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Go to **Follow-up**

Follow-up

- At GN's 3-month review, her HbA_{1c} was 57 mmol/mol (7.4%) and her weight was 83 kg
  - She no longer experienced hunger pangs during the day, and had not experienced hypoglycaemic episodes since starting her new regimen
  - She did not need to perform SMBG and felt confident when driving
- GN's HbA_{1c} level was still above the target recommended by NICE for a person with T2D on dual therapy (i.e. 53 mmol/mol [7.0%])[2]
  - Therefore, her GP discussed options for adding on a further oral glucose-lowering agent to help achieve this HbA_{1c} target and to minimise the risk of developing diabetes-related complications

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Go to **Clinical implications (i)**

SMBG, self-monitoring of blood glucose

Clinical implications (i)

- The symptoms of hypoglycaemia warn an individual of its onset and vary considerably between individuals[22]
  - For example, autonomic symptoms include sweating, palpitations and hunger; neuroglycopenic symptoms include confusion, drowsiness and speech difficulty; these may be accompanied by signs of general malaise, such as headache and nausea[22]
- The glucose level at which an individual becomes symptomatic is highly variable[23]
  - When driving, blood-glucose should always be >5 mmol/L; if SMBG shows a level of ≤5 mmol/L, a snack should be taken before driving; if blood-glucose is <4 mmol/L, or warning signs of hypoglycaemia develop, the driver should not drive[24]
  - In people with T2D, 'hypoglycaemia unawareness' increases with advancing age[25] and with recurrent hypoglycaemic episodes[26]

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Go to **Clinical implications (ii)**

SMBG, self-monitoring of blood glucose; T2D, type 2 diabetes

Clinical implications (ii)

- Weight gain is a major concern for many individuals with type 2 diabetes[27]
  - Obesity and increases in body weight in adults are considered to be among the most important risk factors for T2D[28]
  - For adults with T2D who are overweight, a body weight loss target of 5–10% is recommended by NICE[2]
- Involve adults with T2D in decisions about their individual HbA_{1c} target, and discuss the benefits and risks of drug treatment, and the options available[2]
  - This supports the person with diabetes in making a fully-informed decision[2]

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Go to **Clinical implications (iii)**

T2D, type 2 diabetes

Clinical implications (iii)

- Education is important at all stages of the diabetes journey – at diagnosis and at every review[2]
  - For example, when prescribed a sulphonylurea, GN should have been given advice about using SMBG before driving and what to do in the event of hypoglycaemia[2]
    - She should have been made aware that chocolate is a poor choice for managing hypoglycaemia[29,] and that a readily available source of glucose should be kept to hand when driving[30] (e.g. glucose tablets, sweets and some form of longer-acting carbohydrate kept in the driver's door pocket, rather than in the glove compartment)
- After initiating a monotherapy or dual therapy regimen for a person with T2D, if their agreed HbA_{1c} target is not achieved within 3 months, consider intensifying the regimen, taking into account their age and other relevant factors[4–10]

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SMBG, self-monitoring of blood glucose; T2D, type 2 diabetes

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Prescribing information PI

Prescribing information (i)

TRAJENTA® (linagliptin) 5 mg film-coated tablets

Film-coated tablets containing 5 mg linagliptin. **Indication:** Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Dose and Administration:** 5 mg once daily. If added to metformin, the dose of metformin should be maintained and linagliptin administered concomitantly. When used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia. Renal impairment: no dose adjustment required. Hepatic impairment: pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. Elderly: no dose adjustment is necessary based on age however, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population. Paediatric population: the safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. Take the tablets with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as possible but a double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin; a dose reduction of the sulphonylurea or insulin may be considered. Acute pancreatitis: In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Bullous pemphigoid: If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interactions:** Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates. The risk for clinically meaningful interactions by other medicinal products on linagliptin is low and in clinical studies linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, warfarin, digoxin or oral contraceptives (please refer to Summary of Product Characteristics for information on clinical data). **Fertility, pregnancy and lactation:** Avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for linagliptin. **Undesirable effects:** Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies (frequencies identified from pooled analysis of placebo-controlled studies) in clinical trial and from post-marketing experience. The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data). Very common: hypoglycaemia (combination with/add-on to metformin and sulphonylurea). Common: lipase increased (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin; combination with/add-on to metformin and empagliflozin). Uncommon: nasopharyngitis (monotherapy; combination with/add-on to metformin; combination with/add-on to insulin); hypersensitivity e.g. bronchial hyperreactivity (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); cough (monotherapy; combination with/add-on to metformin; combination with/add-on to insulin); pancreatitis (combination with/add-on to insulin); constipation (combination with/add-on to insulin); rash (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin). Rare: angioedema (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); urticaria (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (monotherapy). Not known: nasopharyngitis (combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); hypersensitivity e.g. bronchial hyperreactivity (combination with/add-on to metformin and empagliflozin); cough (combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); pancreatitis (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); bullous pemphigoid (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (combination with/add-on to insulin). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 28 tablets £33.26. **Legal category:** POM. **MA number:** EU/1/11/707/003. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** April 2017.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

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