Pharmacotherapies to manage diabesity: An update

Caroline Day, Clifford J Bailey

Several pharmacotherapies have recently become available for addition to lifestyle measures to assist the management of coexistent type 2 diabetes and obesity. These are mostly administered as add-on to metformin or as alternative therapies if metformin is not appropriate. The sodium–glucose cotransporter 2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) act by eliminating excess glucose in the urine. These agents provide a non-insulin-dependent mechanism to reduce hyperglycaemia and facilitate weight loss without causing frank hypoglycaemia. Their efficacy requires the individual to have adequate renal function. The glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide, liraglutide, lixisenatide, dulaglutide and albiglutide [the last at the pre-launch stage at the time of writing]) are injected subcutaneously. Different members of the class offer different time courses for their onset and duration of action. Each potentiates insulin secretion and reduces glucagon secretion in a glucose-dependent manner to address prandial glycaemic excursions while avoiding interprandial hypoglycaemia. A satiety effect of these agents assists weight reduction, but delayed gastric emptying can cause initial nausea. The dipeptidyl peptidase-4 inhibitor class now comprises sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. These agents offer similar glucose-lowering efficacy without weight gain or hypoglycaemia by boosting the half-life of endogenous incretins, particularly GLP-1. A fixed-ratio injected combination of insulin degludec with liraglutide (IDegLira) has recently been launched and further agents to address hyperglycaemia and assist weight loss are advancing in development.

Online learning opportunity

See page 23 for details.

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Article points

1. Several pharmacotherapy classes have recently become available for addition to lifestyle measures to assist the management of coexistent type 2 diabetes and obesity: glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors.
2. A fixed-ratio combination of a basal insulin and a GLP-1 receptor agonist has also been recently launched in the UK.
3. Orlistat is, at the time of writing, the only pharmacological anti-obesity drug, but there are medicines in development and under review by European regulators.

Key words

- Dipeptidyl peptidase-4 inhibitors
- Glucagon-like peptide-1 receptor agonists
- Glucose-lowering
- Sodium–glucose cotransporter 2 inhibitors
- Weight loss

Authors

Caroline Day is Editor of *British Journal of Diabetes and Vascular Disease* and Visiting Senior Fellow at Aston University, Birmingham. Clifford J Bailey is Professor of Clinical Science, Aston Medical School, Aston University, Birmingham.

Since our previous review of pharmacotherapy to treat diabesity (Day and Bailey, 2012), the epidemic of coexistent type 2 diabetes with obesity has continued to escalate (International Diabetes Federation, 2013). An individualised management strategy is advocated with lifestyle (mainly diet and exercise) advice initially and throughout. This is supplemented with pharmacotherapy to assist blood glucose control, ideally without weight gain and preferably with weight loss, as well as treatments for comorbidities and to reduce cardiovascular risk (Rajeswaran et al, 2012). Metformin is usually the preferred initial blood glucose-lowering agent as it counters insulin resistance without weight gain and without causing hypoglycaemia (Bailey et al, 2007). Further agents with complementary actions are then added as required (*Figure 1*), aiming to treat both the hyperglycaemia and adiposity (NICE, 2009; Bailey, 2011; Inzucchi et al, 2012; Day, 2013).

In the last 3 years, several new pharmacotherapies have become available to address diabesity. This update considers the role of these therapies to intervene against the diversity of diabesity presentations.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists comprise a class of peptides that bind and activate receptors for the natural incretin hormone GLP-1. They potentiate insulin secretion and reduce glucagon secretion in a glucose-dependent manner,

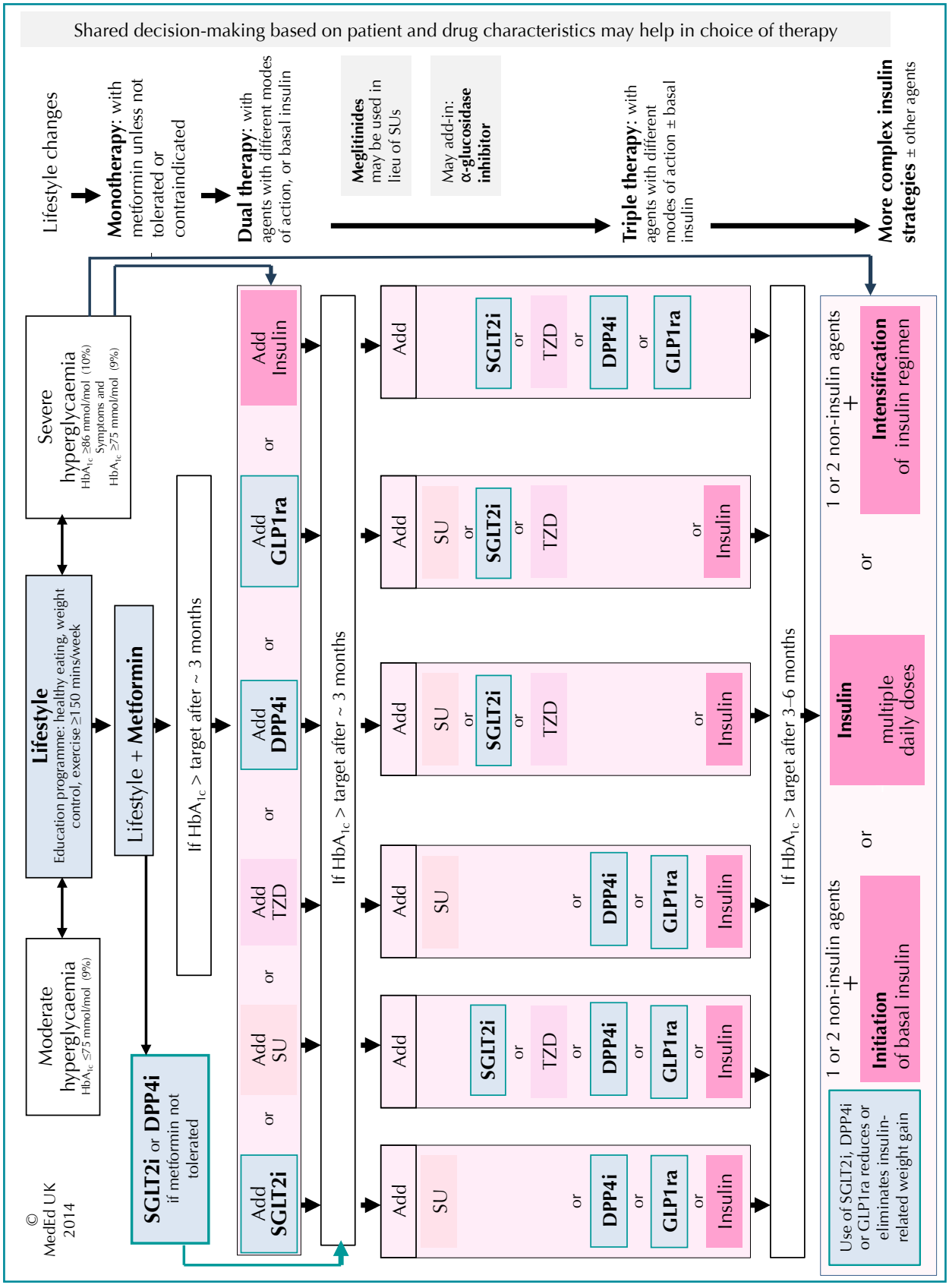

Figure 1. Generalised algorithm for the treatment of hyperglycaemia in type 2 diabetes. Green-shaded options indicate preferred classes of agents to avoid weight gain and preferably facilitate weight loss. This algorithm is based on the position statement of the American Diabetes Association and the European Association for the Study of Diabetes (Inzucchi et al, 2012), NICE clinical guidance (2009) and is adapted from Day (2013).
DPP4i=dipeptidyl peptidase-4 inhibitor; GLP1ra=glucagon-like peptide-1 receptor agonist; SGLT2i=sodium–glucose cotransporter 2 inhibitor; SU=sulphonylurea; TZD=thiazolidinedione.
N.B. The SGLT2 inhibitor dapagliflozin is not recommended for use in combination with pioglitazone (electronic Medicines Compendium, 2014a). Although the SGLT2 inhibitors are licensed for use with other glucose-lowering medicinal products, including insulin, as yet no data have been published in combination with a GLP1 receptor agonist.

Table 1. Glucagon-like peptide-1 (GLP-1) receptor agonists available in the UK and advanced in development.

Agent (Brand)	Dose (by sc injection)	Regimen	Structure/formulation
Exenatide BD (Byetta®)	5/10 mcg	Twice daily before meals	Exendin (GLP-1 analogue)
Lixisenatide (Lyxumia®)	10/20 mcg	Once daily	Exendin analogue
Liraglutide (Victoza®)	0.6/1.2/1.8 mg*	Once daily	GLP-1 linked to a fatty acid
Exenatide QW (Bydureon®)	2 mg	Once weekly	Long-acting formulation of exendin
Dulaglutide (Trulicity®)	0.75/1.5 mg	Once weekly	2 x GLP-1 linked to Fc fragment of IgG4
Albiglutide† (Eperzan®)	30 mg	Once weekly	2 x GLP-1 linked to albumin

Information from the electronic Medicines Compendium (2015a; 2014b; 2015b; 2015c; 2015d).
*NICE (2010) recommends liraglutide up to 1.2 mg/day (not 1.8 mg/day).
†Albiglutide is approved in Europe by the European Commission (European Medicines Agency, 2014), but it is not available in the UK at the time of writing.
BD=twice daily; QW=once a week; sc=subcutaneous.

lowering blood glucose particularly after meals and carrying negligible risk of interprandial or fasting hypoglycaemia. Since GLP-1 receptor agonists delay gastric emptying they may cause temporary nausea in some individuals. This class of agents also exerts satiety effects that facilitate weight loss (Drucker and Nauck, 2006; Meier, 2012; Campbell and Drucker, 2013).

Table 1 lists the available and pre-launch GLP-1 receptor agonists (at the time of writing); they are variously administered twice daily, once daily or once weekly by subcutaneous injection, depending upon their pharmacokinetic properties and formulations. Various published meta-analyses have suggested subtle differences in the glucose-lowering and weight-lowering efficacy of members of the class, although it is difficult to fairly account for variability in patient populations, baseline characteristics, trial designs and data analyses (Amori et al, 2007; Monami et al, 2009; Aroda et al, 2012). In randomised trials, the average reduction of HbA_{1c} is typically in the range of 9–16 mmol/mol (0.8–1.5%), occasionally greater, and the weight-lowering effect is mostly about 2–3 kg (e.g. Aroda et al, 2012).

A recent audit of "real life" use of exenatide twice daily and liraglutide in the UK has confirmed the results seen in clinical trials and noted that while a majority of people respond to these agents, they may have little or no effect in some individuals (Thong et al, 2014). Indeed, NICE (2009) recommends that treatment with these agents should only be continued beyond 6 months if HbA_{1c} is reduced by ≥11 mmol/mol (≥1%) and there is ≥3% weight loss. Since there is no clear marker to predict who will respond, as with most glucose-lowering treatments, it is appropriate to "try and see" on an individual basis. A finger-stick measure of glucose control after 2–4 weeks can be a useful indicator of longer-term responsiveness. We suggest that, even if treatment with a GLP-1 receptor agonist is not lowering *both* glucose and weight to the extent required by NICE, the agent may still be preventing increases in these factors (or improving one of them). Furthermore, discontinuation of the agent may leave insulin as the only option, because such individuals have usually already exhausted suitable oral agents. Advice from NICE (2009; 2010; 2012; 2013) to generally restrict use of a GLP-1 receptor agonist to a BMI ≥35 kg/m^2 in individuals of European descent (with adjustment for other ethnic groups) can, we should remember, be over-ridden by clinical need.

To date, responders have shown good durability of glucose control and weight reduction during exenatide once-weekly treatment for up to 6 years (Diamant et al, 2014; Henry et al, 2014). Although pre-clinical data suggest that this and other GLP-1 receptor agonists can improve beta-cell mass (Tahrani et al, 2011), there is, as yet, no obvious evidence in human type 2 diabetes

that the progressive decline in beta-cell function can be reversed.

Nausea remains an initial tolerability factor for some individuals receiving a GLP-1 receptor agonist, but this is mostly temporary (electronic Medicines Compendium [eMC], 2014b; 2015a; 2015b; 2015c; 2015d). Questions concerning a possible association between GLP-1 receptor agonists and acute pancreatitis have been asked in recent years. Present data from registration trials, insurance databases, audits and post-marketing studies have not indicated any substantive increase in risk, but careful monitoring is ongoing (Egan et al, 2014). Accordingly, regulators have advised caution in patients with a history of pancreatitis and discontinuation if pancreatitis is suspected or confirmed (European Medicines Agency [EMA], 2013; Medicines and Healthcare products Regulatory Agency, 2013; US Food and Drug Administration, 2013).

Fixed-ratio combinations

Emerging clinical experience and controlled studies have noted the benefits of combination therapy using a GLP-1 receptor agonist together with a basal insulin (Holst and Vilsbøll, 2013). To simplify the administration of two such agents into a single injection, a fixed-ratio combination, IDegLira (Xultophy®), has recently been launched in the UK (eMC, 2014c). IDegLira combines 50 units of the long-acting insulin analogue degludec with 1.8 mg of the GLP-1 receptor agonist liraglutide as the maximum recommended daily dose. This is titrated up in the same way as the titration of insulin alone; thus, for every 1 unit of insulin injected, the individual also receives 0.036 mg liraglutide at the same time. In a 1-year randomised clinical trial with obese and overweight people with type 2 diabetes inadequately controlled on metformin with or without pioglitazone (the DUAL-I trial), IDegLira reduced HbA_{1c} from a baseline of 68 mmol/mol (8.3%) by 21 mmol/mol (1.8%) without incurring the weight gain seen with insulin alone (Gough et al, 2014a; 2014b). The glucose-lowering effect was greater than achieved with a higher dose of insulin degludec (IDeg) alone, indicating an insulin-sparing effect of IDegLira (*Table 2*), and there were about one-third fewer recorded episodes of hypoglycaemia with IDegLira than IDeg alone (Gough et al, 2014a). Other fixed-ratio combinations of a basal insulin with a GLP-1 receptor agonist (such as insulin glargine with lixisenatide – LixiLan) are in development (Rosenstock et al, 2014).

Table 2. One-year trial in people with type 2 diabetes randomised to once-daily subcutaneous injection of insulin degludec (IDeg), liraglutide (Lira) or a fixed-ratio combination of these agents (IDegLira) as add-on to metformin with or without pioglitazone (Gough et al, 2014a; 2014b). Values shown are means after 1 year, with changes being relative to baseline*.

	IDeg (*n*=333)	Lira (*n*=313)	IDegLira (*n*=665)
Change in HbA_{1c} (mmol/mol) (%)	–15 –1.4	–12 –1.2	–21 –1.8
FPG (mmol/L)	6.0	7.3	5.7
Change in weight (kg)	+2.4	–3.0	–0.4
Insulin dose (units/day)	62	—	39

*Baseline HbA_{1c} 68 mmol/mol (8.3%), baseline body weight 87 kg and baseline BMI 31.2 kg/m². During the first 26 weeks of this study, the number of confirmed hypoglycaemic events per patient year was 1.8 for IDegLira, 0.2 for liraglutide and 2.6 for insulin degludec (Gough et al, 2014a). –=decrease change; +=increase change; FPG=fasting plasma glucose.

Table 3. Dipeptidyl peptidase-4 inhibitors available in the UK.

Agent (Brand)	Dosage	$t_{1/2}$ (hours)	Elimination	Metabolite
Sitagliptin (Januvia®)	25/50/100 mg OD	~12.4	~87% renal ~13% faeces	Trivial metabolism; mostly eliminated unchanged
Vildagliptin (Galvus®)	50 mg BD	~3	~85% renal ~15% faeces	Inactive metabolites
Saxagliptin (Onglyza®)	2.5/5.0 mg OD	~2.5 (~3.1 for metabolites)	~75% renal (includes metabolites) ~22% faeces	Active main metabolite
Linagliptin (Trajenta®)	5 mg OD	~12	~5% renal >80% faeces	Trivial metabolism; mostly eliminated by liver
Alogliptin (Vipidia®)	6.25/12.5/25 mg OD	~21	~76% renal ~13% faeces	Trivial metabolism; mostly excreted unchanged

Information from the electronic Medicines Compendium (2014d; 2014e; 2014f; 2014g; 2015e). BD=twice daily; OD=once daily.

Dipeptidyl peptidase-4 inhibitors

The enzyme dipeptidyl peptidase-4 (DPP-4) degrades endogenous incretin hormones such as GLP-1; thus, DPP-4 inhibitors increase the circulating levels of endogenous incretin hormones by reducing their rate of loss from the circulation.

Five DPP-4 inhibitors are available in the UK at the time of writing (*Table 3*). Meta-analyses of controlled trial (Esposito et al, 2014) and "real life"

Table 4. Single tablet fixed-dose combinations.

Tablet	Components	Strengths (mg)
Fixed doses with older agents		
Competact®	Pioglitazone + metformin	15:850
Fixed doses with dipeptidyl peptidase-4 inhibitors		
Eucreas®	Vildagliptin + metformin	50:850; 50:1000
Janumet®	Sitagliptin + metformin	50:1000
Jentadueto®	Linagliptin + metformin	2.5:850; 2.5:1000
Komboglyze®	Saxagliptin + metformin	2.5:850; 2.5:1000
Vipdomet®	Alogliptin + metformin	12.5:1000
Fixed doses with sodium–glucose cotransporter 2 inhibitors		
Vokanamet®	Canagliflozin + metformin	50:850; 50:1000
Xigduo®	Dapagliflozin + metformin	5:850; 5:1000

Information from electronic Medicines Compendium (2014h; 2014i; 2014j; 2014k; 2014l; 2014m; 2015f; 2014n; 2014o; 2015g).

Table 5. Sodium–glucose cotransporter 2 inhibitors available in the UK.

Agent (Brand)	Dosage	$t_{1/2}$ (mean in hours)*	Elimination	Metabolite
Dapagliflozin† (Forxiga®)	5/10 mg OD	12.9 for 10 mg	~75% renal ~21% faeces	Mostly glucuronide metabolites (inactive)
Canagliflozin (Invokana®)	100/300 mg OD	*For 100 mg:* 10.6±2.13 *For 300 mg:* 13.1±3.28	~33% renal ~52% faeces	~30% glucuronide metabolites (inactive)
Empagliflozin (Jardiance®)	10/25 mg OD	12.4 (for both dosages)	~54% renal (includes metabolites) ~41% faeces	<30% glucuronide metabolites (inactive)

Information from electronic Medicines Compendium ([eMC], 2014a; 2014p; 2014q; 2015h; 2015i).
*±standard deviation, where reported.
†Dapagliflozin is not to be used in combination with pioglitazone (eMC, 2014a).
OD=once daily.

databases indicate similar glucose-lowering efficacy across the class, with decreases in HbA_{1c} by about 7–11 mmol/mol (0.6–1.0%). DPP-4 inhibitors are weight neutral and carry a very low risk of frank hypoglycaemia, due to the glucose-dependent nature of the incretin effect (Deacon, 2011). Although there are differences in pharmacokinetic properties, the only practical differences noted by most prescribers are that they are all once daily except vildagliptin (twice daily), and all require dose reduction with impaired renal function except linagliptin.

Although DPP-4 inhibition is known to affect the half-lives of various hormones and signalling peptides beyond the incretin system (Flatt et al, 2008), extensive use of DPP-4 inhibitors has raised minimal safety issues (Goossen and Graber, 2012). Post-marketing cardiovascular safety studies have recently been reported for saxagliptin and alogliptin, noting a small increase in the number of individuals with heart failure who were hospitalised, and this is receiving further investigation (Scirica et al, 2013; White et al, 2013). There were also more reports of acute pancreatitis in the active arms than the placebo arms, but the absolute numbers were small and large database analyses have not confirmed these issues (Patil et al, 2012).

Several fixed-dose combinations of DPP-4 inhibitors with metformin are available (see *Table 4*), and these provide a convenient opportunity to intensify treatment without increasing the pill burden (Bailey and Day, 2009). For the future, once-weekly DPP-4 inhibitors are in development (Biftu et al, 2014).

Sodium–glucose cotransporter 2 inhibitors

There are now three sodium–glucose cotransporter 2 (SGLT2) inhibitors available in the UK (*Table 5*). These agents competitively inhibit the reabsorption of filtered glucose from the proximal tubules, eliminating up to about 100 g glucose daily in the urine (Bailey and Day, 2010). Because the mode of action is independent of insulin secretion or action, the glucose-lowering efficacy of these agents is seen at any stage during the natural history of type 2 diabetes provided that the individual has adequate renal function.

The effectiveness of SGLT2 inhibitors to generate glycosuria is dependent on adequate renal filtration indicated by an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 for maximal dosing. Dosage reduction is required for canagliflozin and empagliflozin down to eGFR 45 mL/min/1.73 m^2. There are no data to indicate renal damage with these agents (Bailey and Day, 2014).

Clinical trials, some up to 4 years in duration, have consistently shown a reduction of HbA_{1c} in the range of 6–11 mmol/mol (0.5–1%) as monotherapy or add-on to other glucose-lowering treatments including insulin (Tahrani et al, 2013). The renal elimination of glucose also assists weight loss (typically 2–3 kg) and may contribute to a small reduction in blood pressure (similar to a low-dose thiazide diuretic). By reducing glucotoxicity and lowering body weight, SGLT2 inhibitors can reduce the dose requirement

for other drugs including insulin (Tahrani et al, 2013). The glucosuria increases the risk of genital and urinary tract infections, but evidence to date indicates that risk can be limited with appropriate patient education and managed by standard procedures. While analyses of cardiovascular events during pre-registration clinical trials have been well within the requirements of regulatory agencies, long-term post-marketing cardiovascular safety studies are in progress.

SGLT2 inhibitors are metabolised by a uridine system. This avoids interactions with most commonly used drugs including other classes of glucose-lowering agents (Bailey and Day, 2014), and fixed-dose combinations of SGLT2 inhibitors with metformin are licensed (see *Table 4*).

Anti-obesity agents

Although weight reduction is a key part of the treatment strategy for diabesity, there is limited access in Europe to pharmacotherapies that are primarily directed against adiposity. Orlistat is the only agent specifically indicated for weight loss in the UK, and this has been shown to modestly assist glycaemic control in people with type 2 diabetes (Yanovski and Yanovski, 2013). Several additional anti-obesity agents have been approved in the US, and others are in advanced development (Scheen and Van Gaal, 2014). Of note, a single daily subcutaneous injection of 3 mg liraglutide is, at the time of writing, under review by European regulators as a treatment for obesity (EMA, 2015). A 1-year study (the SCALE™ trial) in obese individuals (baseline weight 106 kg, BMI 37 kg/m^2) with type 2 diabetes showed a 5.9% weight loss with liraglutide compared with 2% for placebo. Half of the liraglutide group achieved >5% weight loss, and 22% achieved >10% weight loss. The weight loss in the liraglutide group was accompanied by a reduction of HbA_{1c} by 14 mmol/mol (1.3%) versus 3 mmol/mol (0.3%) with placebo from a baseline HbA_{1c} of 63 mmol/mol (7.9% [Davies et al, 2014]).

Conclusions

Patient-centred "personalised" care for diabesity remains founded on appropriate lifestyle advice to address adiposity and hyperglycaemia, with attention to cardiovascular risk and treatment of comorbidities. Pharmacotherapy to improve glycaemic control without weight gain typically begins with metformin followed by add-on of a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 receptor agonist as appropriate. Alternative approaches not discussed in this review may be considered for morbidly obese people, notably bariatric surgery and intensive dietary interventions.

Among agents primary directed to reduce blood glucose, the SGLT2 inhibitors and GLP-1 receptor agonists facilitate weight loss, while the DPP-4 inhibitors are generally weight neutral or produce very modest weight reduction. It is emphasised that early intervention is important to gain the long-term benefits of glycaemic control and to address the plethora of debilitating complications that accompany protracted obesity. ■

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. A 57-year-old overweight man has developed type 2 diabetes. His HbA_{1c} remains moderately elevated above target, despite 3 months of dietary and lifestyle changes. According to current evidence, which is the SINGLE MOST appropriate first-line therapy? Select ONE option only.

A. Canagliflozin
B. Gliclazide
C. Liraglutide
D. Metformin
E. Pioglitazone

2. Which of the following statements is NOT correct about sodium–glucose cotransporter 2 (SGLT2) inhibitors? Select ONE option only.

A. Due to their mode of action, there is an increased risk of genital and urinary tract infections
B. There are three SGLT2 inhibitors currently available in the UK
C. They are injectable
D. They can be used as a monotherapy
E. They can reduce the dose requirement of other antidiabetes drugs

3. "Reduction in the rate of loss of endogenous incretin hormones" BEST describes the mechanism of action of which ONE of the following classes of antidiabetes agents? Select ONE option only.

A. Biguanides (i.e. metformin)
B. Dipeptidyl peptidase-4 (DPP-4) inhibitors
C. Glucagon-like peptide 1 (GLP-1) receptor agonists
D. SGLT2 inhibitors
E. Sulphonylureas

4. Based on randomised control trials, what is the average predicted weight-lowering effect (over the time-frame of the trial) in a person with type 2 diabetes starting a GLP-1 receptor agonist? Select ONE option only.

A. <1 kg
B. 2–3 kg
C. 4–5 kg
D. 5–7.5 kg
E. >10 kg

5. According to NICE guidance, what is generally the MINIMUM threshold reduction in HbA_{1c} required after 6 months of GLP-1 receptor agonist treatment in order to justify continued treatment (if the weight loss target is also met)? Select ONE option only.

A. 5 mmol/mol (0.45%)
B. 11 mmol/mol (1%)
C. 15 mmol/mol (1.45%)
D. 21 mmol/mol (1.9%)
E. 25 mmol/mol (2.3%)

6. Which of the following groups of diabetes treatments is MOST appropriately referred to as being associated with weight loss? Select ONE option only.

A. DPP-4 inhibitors
B. Insulins
C. SGLT2 inhibitors
D. Sulphonylureas
E. Thiazolidinediones (i.e. pioglitazone)

7. A 71-year-old overweight man with type 2 diabetes and chronic kidney disease stage 4 requires an antidiabetic agent. His HbA_{1c} is 74 mmol/mol (8.9%). Which is the SINGLE MOST appropriate INITIAL medication? Select ONE option only.

A. Dapagliflozin
B. Exenatide
C. Glipizide
D. Linagliptin
E. Metformin

8. Eucreas®, Janumet®, Vokanamet® and Xigduo® are all fixed-dose combination antidiabetes agents. Which ONE of the following do they ALL contain? Select ONE option only.

A. A biguanide
B. A DPP-4 inhibitor
C. A SGLT2 inhibitor
D. A sulphonylurea
E. A thiazolidinedione

9. Which class of antidiabetes agents requires adequate renal filtration in order to be efficacious? Select ONE option only.

A. Sulphonylureas
B. Meglitinidies
C. GLP-1 receptor agonists
D. DPP-4 inhibitors
E. SGLT2 inhibitors

10. A 52-year-old woman with type 2 diabetes is now stepping up to triple therapy with metformin, sitagliptin and dapagliflozin because of persistent hyperglycaemia (HbA_{1c} 75–86 mmol/mol [9–10%]). What is generally the MAXIMUM recommended time interval to achieve an agreed HbA_{1c} target before consideration of insulin initiation? Select ONE option only.

A. 1 month
B. 3 months
C. 6 months
D. 9 months
E. 12 months