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Hyperglycaemia in type 2 diabetes: Newer blood glucose-lowering therapies – update

Neil Munro

Long-established therapies for reducing hyperglycaemia in type 2 diabetes include biguanides, sulphonylureas, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors. Improved understanding of the "incretin" effect has enabled development of glucose-lowering therapies that overcome some of the unwanted effects of earlier oral agents. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors are associated with weight loss, or weight neutrality, and are less likely to cause hypoglycaemia than many glucose-lowering therapies currently used in clinical practice owing to their glucose-dependent mode of action. This article updates and replaces the previous version, published in 2009.

Learning objectives

After reading this article, the participant should be able to:

1. Explain the incretin effect and how it has been explored therapeutically for the treatment of type 2 diabetes.
2. Outline the use of glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors in practice, referring to national guidance.
3. Describe the glucose-lowering mechanism of therapies in the pipeline.

Key words

- Blood glucose lowering
- DPP-4 inhibitors
- GLP-1 receptor agonists

Neil Munro is a GP, Capelfield Surgery, Claygate, and an Associate Specialist in Diabetes at the Beta Cell Diabetes Centre, Chelsea and Westminster Hospital Foundation Trust, London. He is also affiliated with the CSRI Warwick Medical School, Warwick, and the Diabetes Therapies Evaluation Network (DTENet).

Several classes of agents are now available to reduce hyperglycaemia in type 2 diabetes. Established therapies including biguanides, sulphonylureas, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors are now supplemented by therapies whose actions are mediated through the incretin effect – glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

No single agent, or class of drug, will suit all people. In selecting treatments for an individual with type 2 diabetes, a careful balance has to be drawn between efficacy, unwanted effects, including hypoglycaemia and weight gain, and adverse events. In licensing, drugs regulators have to draw a fine line between making new therapies available as quickly as possible and ensuring that the preparations lack significant adverse effects when used in routine clinical practice. The consequences of long-term use of glucose-lowering therapies, in terms of durability and safety, are difficult to predict accurately. Practical aspects, such as frequency of dosing, method of administration, monitoring requirements, drug interactions and

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cost-effectiveness also feed into this complex and individualised decision-making process. Straightforward management algorithms and protocols need increasingly to take account of wider choices and enable shared decisions on optimal therapy strategies between people with diabetes and their professional carers. The complexity of this decision-making is likely to increase as newer therapies with novel modes of action become available for use in routine clinical practice.

Intense post-marketing surveillance of some existing agents has provided further information on their utility and safety in clinical practice. The withdrawal of rosiglitazone following a review by Nissen and Wolski (2007) has heightened regulators' concerns about drug safety both before and after licensing. Newer therapies now require ever more expensive phase III trials, including large cardiovascular safety studies, as intrinsic elements of the licensing process.

This module describes the development path and licensing trials for the newer blood glucose-lowering agents, with an emphasis on the agents currently available to prescribers in the UK. Post-marketing trial evidence is largely unavailable for these agents, although several multicentre trials are in their preliminary phases.

In addition, the module covers key mechanisms currently being explored that may result, over the next 10 years, in the emergence of therapies with novel modes of action, further expanding the palette of agents available for clinical use.

The incretin system

Incretin hormones are peptides released from the intestinal tract in response to mixed meals and they contribute to glucose homeostasis by promoting glucose-dependent insulin secretion. The incretin effect is observed experimentally when insulin responses to oral and intravenous glucose loads are compared. An enhanced response is seen with oral, as opposed to parenteral, glucose.

The role an incretin mechanism might play in glucose homeostasis was first proposed as far back as the 1930s (La Barre, 1932). It was not until the 1960s, however, that researchers demonstrated greater stimulation of insulin when glucose was given orally rather than intravenously at equivalent doses (Elrick et al, 1964; Perley and Kipnis, 1967). Results indicated the presence of gastrointestinal hormonal mediated action that enhanced postprandial insulin secretion in response to oral glucose loading. Eisentraut and Unger described this "intestinal secretion of insulin" as the "incretin" effect (Creutzfeldt and Ebert, 1985).

Two hormones secreted from the gastrointestinal tract account for over 50% of the incretin effect of a mixed meal. They rapidly stimulate insulin release in the presence of hyperglycaemia. The hormones are GLP-1, with 30 amino acids, and glucose-dependent insulinotropic polypeptide (GIP), with 42 amino acids (McIntyre et al, 1964; Nauck et al, 1986). GIP is derived from the K-cells located in the jejunum and responds more to dietary fat than to glucose (Levy, 2006). In type 2 diabetes the beta-cell response to GIP is largely lost, but GLP-1 receptor sensitivity remains. The reasons for reduced GIP responsiveness remain unclear but may be associated with reduced GIP receptor expression in people with significant insulin resistance (Rudovich et al, 2005).

GLP-1 is secreted by the L-cells in the ileum, predominantly in the presence of glucose. This occurs in association with neural signalling arising from food stimulus. These mechanisms induce insulin secretion through direct activation of G-protein-coupled receptors (GPRs) expressed on pancreatic beta-cells (Vilsbøll and Holst, 2004). GLP-1 cannot trigger insulin release by itself; its insulinotropic effect is dependent on ambient glucose. At glucose levels close to the threshold for the triggering of insulin secretion, GLP-1 has very little effect (Triplitt et al, 2006).

In addition to its glucose-dependent action on insulin secretion, GLP-1 has been shown to suppress glucagon secretion, delay gastric emptying and induce satiety and a sense of fullness with resultant reduction in food intake (Levy, 2006). Elevated glucagon levels are found in people with type 2 diabetes and contribute to background and postprandial hyperglycaemia. By direct action on islet alpha-cells GLP-1 reduces excess glucagon secretion

Page points

1. Straightforward management algorithms and protocols need increasingly to take account of wider choices and enable shared decisions on optimal therapy strategies between people with diabetes and their professional carers.
2. Incretin hormones are peptides released from the intestinal tract in response to mixed meals and they contribute to glucose homeostasis by promoting glucose-dependent insulin secretion.
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CPD module

Page points

1. GLP-1 is degraded (and inactivated) in 1–2 minutes by dipeptidyl peptidase-4 (DPP-4), a ubiquitous intracellular enzyme.
2. GLP-1 receptor agonists that are resistant to degradation by DPP-4 (owing to alterations in their molecular structure) and DPP-4 inhibitors, that promote physiological secretion of endogenous GLP-1 have been developed.
3. Exenatide was first launched in the USA in 2005 and in the UK in 2007. It is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster (a poisonous Mexican lizard) that has a 53% homology with human GLP-1.
4. Liraglutide is an albumin-bound analogue of human GLP-1 that is DPP-4 resistant and has been in clinical use since July 2009.
5. Exenatide once weekly is the first once-weekly GLP-1 receptor agonist to become available for clinical use in the UK. The formulation consists of injectable microspheres of exenatide (2 mg) and poly(D,L-lactic-co-glycolic acid), a biodegradable polymer, allowing slow and controlled drug release from the subcutaneous tissue.

without impacting on its protective effect in hypoglycaemia.

GLP-1 is degraded (and inactivated) in 1–2 minutes by DPP-4, a ubiquitous intracellular enzyme. This rapid degradation reduces the usefulness of human GLP-1 in clinical practice (since it would have to be continually infused in order to retain its biological action) and has led to the development of GLP-1 receptor agonists that are resistant to degradation by DPP-4 (owing to alterations in their molecular structure) and DPP-4 inhibitors, that promote physiological secretion of endogenous GLP-1.

Current and future GLP-1 receptor agonists

Three GLP-1 receptor agonists are currently available for use in clinical practice in the UK – exenatide twice daily, liraglutide and exenatide once weekly.

Exenatide was first launched in the USA in 2005 and in the UK in 2007. It is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster (a poisonous Mexican lizard) that has a 53% homology with human GLP-1. It is administered twice daily by subcutaneous injection given within an hour of morning and evening meals. There are two pen devices, one delivering a dose of 5 µg and the other 10 µg. Each will deliver a month's worth of agent. Initiation in the first month is with 5 µg twice daily, increasing to 10 µg thereafter (Electronic Medicines Compendium, 2012e).

Liraglutide is an albumin-bound analogue of human GLP-1 that is DPP-4 resistant and has been in clinical use since July 2009. It has a duration of action that allows once-daily administration. It can be administered at any time during the day. It has dose regimen that escalates weekly, starting at 0.6 mg daily, and rising to 1.2 mg daily, or potentially 1.8 mg daily. All doses are delivered through a single pen device (Electronic Medicines Compendium, 2012f).

Exenatide once weekly is the first once-weekly GLP-1 receptor agonist to become available for clinical use in the UK. The formulation consists of injectable microspheres of exenatide (2 mg) and poly(D,L-lactic-*co*-glycolic acid), a biodegradable polymer, allowing slow and controlled drug release from the subcutaneous tissue (Tracey, 1999). The polymer has established use in other slow-release preparations and in absorbable sutures.

As with other glucose-lowering drugs there are responders and non-responders. The ability of the beta-cell to secrete insulin as a result of GLP-1 activation determines the glucose-lowering potential of this class of drug in individual people. A shorter duration of diabetes, in the author's experience, may give some indication of a higher likelihood of response, although some people with long disease duration demonstrate insulin release following GLP-1 stimulation. It remains difficult, however, to accurately identify those who will respond optimally to this class of drug. There is some variation in the efficacy of these agents across phase III and post-licensing trials. Weight loss is noted consistently in study populations (Bailey, 2011). While this is not the licensed indication of the GLP-1 receptor agonists, it is a property that is attractive to both clinician and patient. Side effects are predominantly gastrointestinal but infrequently lead to cessation of therapy. Patient preference and prescriber experience play a large part in ensuring that therapies are tailored to the needs and expectations of each individual.

Recent licence extensions allow insulin detemir to be added to liraglutide (Electronic Medicines Compendium, 2012d) and exenatide twice daily to be added to basal insulin or to be continued when a basal insulin is added to existing therapy (Electronic Medicines Compendium, 2012e) in people with type 2 diabetes. These combinations are logical in terms of complementary modes of action and the potential for insulin sparing. However, care should be taken to avoid reducing insulin significantly in the presence of evolving beta-cell failure.

Several GLP-1 receptor agonists are in development including lixisenatide (daily administration), albiglutide, dulaglutide, LY2428757, semaglutide and CJC-1134-PC (all weekly administration). Taspoglutide is being reformulated following tolerability problems in phase III trials (UK Medicines Information).

As peptides, GLP-1 receptor agonists are

Table 1. Molecule-specific product profiles of UK commercially available DPP-4 inhibitors, based on drug Summaries of Product Characteristics. Correct at time of going to print.

	Sitagliptin (EMC, 2012a)	Vildagliptin (EMC, 2012b)	Saxagliptin (EMC, 2012c)	Linagliptin (EMC, 2011c)
Summary of licensed indications (please consult Summaries of Product Characteristics for full details)	Monotherapy (where MET is not appropriate), dual oral therapy (with MET, SU or TZD), triple oral therapy (with MET+SU or MET+TZD) or add-on to insulin*	Monotherapy (where MET is not appropriate) or dual oral therapy (with MET, SU or TZD)*	Dual oral therapy (with MET, SU or TZD) or add-on to insulin*	Monotherapy (where MET is not appropriate), dual oral therapy (with MET) or triple oral therapy (with MET+SU)*
Dose*	100 mg QD (highest licensed dose) **Availability in fixed-dose combination** 50 mg sitagliptin and 1000 mg MET hydrochloride BD (EMC, 2011a)	50 mg BD when used with MET or a TZD 50 mg QD when used with an SU **Availability in fixed-dose combination** 50 mg of vildagliptin and 850 mg or 1000 mg of MET hydrochloride BD (EMC, 2011b)	5 mg QD (highest licensed dose)	5 mg QD
Patients with renal impairment*	**Mild (CrCl ≥50 mL/min)** No dose adjustment is required **Moderate (≥30 to <50 mL/min)** 50 mg QD **Severe (<30 mL/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis** 25 mg QD Assessment of renal function is recommended prior to initiation and periodically thereafter	**Mild (CrCl 50 to <80 mL/min)** No adjustment necessary **Moderate (30 to <50 mL/min) or severe (<30 mL/min)** 50 mg QD **End-stage renal disease requiring haemodialysis** 50 mg QD with caution	**Mild (CrCl >50 to ≤80 mL/min)** No dose adjustment is required **Moderate (≥30 to ≤50 mL/min) or severe (<30 mL/min)** 2.5 mg QD Experience in patients with severe renal impairment is very limited **End-stage renal disease requiring haemodialysis** Not recommended owing to limited experience Assessment of renal function is recommended prior to initiation and should be done periodically thereafter	No dose adjustment is required
Patients with hepatic impairment*	No dose adjustment is required in mild or moderate hepatic impairment Has not been studied in severe hepatic impairment	Should not be used in patients with hepatic impairment, including where liver enzymes are elevated (ALT or AST >3×ULN) Liver function tests should be performed prior to the initiation of treatment Liver function should be monitored during treatment at 3-month intervals during the first year and periodically thereafter	Should be used with caution in moderate impairment Not recommended in severe hepatic impairment	Pharmacokinetic studies suggest that no dose adjustment is required Clinical experience in such patients is lacking

ALT=alanine aminotransaminase; AST=aspartate transaminase; BD=twice daily; CrCl=creatinine clearance; EMC=*Electronic Medicines Compendium*; MET=metformin; QD=once daily; SU=sulphonylurea; TZD=thiazolidinedione; ULN=upper limit of normal.

*The information is abbreviated from Summaries of Product Characteristics, which should be consulted for full details.

destroyed by gastric acidity and currently need to be administered by subcutaneous injection. Novel mechanisms in development for administering GLP-1 receptor agonists include 3-monthly implants of exenatide using the Duros® implantable system, inhalation using Technosphere® delivery devices and transdermal patches (Qian et al, 2009).

Table 2. Current treatments for type 2 diabetes (Bailey, 2011).

Agent	Main mechanisms of action	Reduction in HbA_{1c} (mmol/mol [percentage points])	Reduction in FPG (mmol/L)	Body weight	Cautions and contraindications*
Agents administered orally					
Metformin	Reduces insulin resistance† and hepatic glucose output; increases peripheral glucose utilisation and glucose turnover between intestine and liver	~11–22 (~1–2)	1–4	↓/–	Gastrointestinal side effects; lactic acidosis (rare); contraindicated if renal impairment or any hypoxaemic condition
Sulphonylureas	Directly increase insulin secretion‡; bind to SUR1 on beta-cells	~11–22 (~1–2)	2–4	↑	Risk of severe hypoglycaemia; use restricted by severe liver disease, renal disease or porphyria
Meglitinides	Directly increase insulin secretion‡,§; bind to benzamido site on SUR1; rapid onset, short duration of action	~5–16 (~0.5–1.5)	1–3	↑/–	Less of a risk of hypoglycaemia (than with sulphonylureas); use restricted by liver disease or severe renal disease
DPP-4 inhibitors	Increase insulin secretion‡; prevent degradation of incretin hormones by DPP-4, which allows longer potentiation of nutrient-induced (prandial) insulin secretion	~6–16 (~0.6–1.5)	0.6–1.2	–	Small risk of hypoglycaemia (seldom severe), mostly when used with other glucose-lowering agents; use may be restricted by substantial renal disease or liver disease (see *Table 1*)
Thiazolidinediones	Increase insulin action† and adipogenesis; stimulate PPAR-gamma; alter glucose–fatty acid cycle	~6–22 (~0.6–2.0)	2–3	↑	Caution concerning heart failure, oedema, fluid retention, anaemia and fractures; precluded by cardiac disease, severe liver disease or renal disease
Alpha glucosidase inhibitor	Slows carbohydrate digestion‖	~6–11 (~0.5–1.0)	~0.5	–	Gastrointestinal discomfort; avoid if intestinal diseases, severe kidney or liver disease
Agents administered by subcutaneous injection					
GLP-1 receptor agonists	Increase insulin secretion‡ and decrease glucagon secretion; resistant to degradation by DPP-4; potentiate nutrient-induced (prandial) insulin secretion	~6–22 (~0.5–2.0)	0.7–2.5	↓	Nausea; risk of hypoglycaemia when used with other glucose-lowering agents; avoid in severe renal disease or gastroparesis; stop if pancreatitis is suspected
Insulins	Decrease lipolysis and hepatic glucose output; increase peripheral glucose uptake, storage and utilisation	Adjust dose and regimen as needed	Adjust dose and regimen as needed	↑	Risk of severe hypoglycaemia; substantial lifestyle adjustments needed; glucose monitoring

DPP-4=dipeptidyl peptidase-4; FPG=fasting plasma glucose; GLP-1=glucagon-like peptide-1; PPAR-gamma=peroxisome proliferator-activated receptor gamma; SUR1=sulphonylurea receptor 1; ↑=increase; ↓=decrease; –=no change.

*Most agents can rarely cause hypersensitivity reactions.
†Requires presence of circulating insulin.
‡Requires presence of a functional beta-cell mass.
§Take with meals to reduce the risk and severity of hypoglycaemia.
‖Take with meals rich in complex carbohydrate.

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Current and future DPP-4 inhibitors

Four DPP-4 inhibitors are currently available for use in clinical practice in the UK – sitagliptin, vildagliptin, saxagliptin and linagliptin.

Sitagliptin was the first in the class to become available for use in the UK following licensing approval in 2007 (Electronic Medicines Compendium, 2012a). Since then, vildagliptin, saxagliptin and, more recently, linagliptin have been added to the therapeutic armamentarium. Others in advanced development include alogliptin, dutogliptin and gemigliptin. Interestingly, berberine, a common herbal dietary supplement, inhibits DPP-4. This partly explains its glucose-lowering effect (Al-Masri et al, 2009).

As oral agents that inhibit degradation of endogenous GLP-1 by DPP-4, their glucose-lowering action is less pronounced than that of the GLP-1 receptor agonists, whose pharmacological dosing produces levels of GLP-1 receptor agonism several times greater than those seen with DPP-4 inhibitors (Holst et al, 2008). However, the side-effect profile is also less pronounced (probably as a result of lower levels of GLP-1 receptor agonism) and the class is, in general, well tolerated (Holst et al, 2008). In addition, DPP-4 inhibitors have the distinct advantage of being oral preparations.

Recent developments have seen extensions of licensed use in various levels of renal impairment. Whether there is a need to reduce drug dosage or perform additional monitoring with declining renal function depends on the route of elimination of the agent, and there are differences within the class in this regard (*Table 1*). There is some variation in the licence for co-administration with other glucose-lowering agents. In addition, some metformin combinations have become available for clinical use.

Selecting agents in practice

There is now an extensive range of glucose-lowering agents available for use in daily diabetes practice. Ideally decisions should be based on a balance between efficacy, utility and adverse effects.

Trial evidence

Bailey (2011) has summarised the characteristics of the incretin agents in relation to existing glucose-lowering treatments (*Table 2*).

Reid (2012) has recently summarised some of the major trials comparing agents in the incretin class. The goals and designs of these are summarised in *Table 3*, and the principal findings are provided in Reid's paper. The article appeared in the American journal *Clinical Diabetes* and the approval of exenatide once weekly in the USA (Amylin, 2012) came subsequent to its publication. In addition, vildagliptin has not been launched in the USA. Thus, the list of studies considered in the paper is not exhaustive. Readers should note, for instance, that exenatide once weekly has been compared with other incretin therapies (exenatide twice daily, liraglutide 1.8 mg and sitagliptin) in a series of head-to-head trials as part of the DURATION series (Drucker et al, 2008; Bergenstal et al, 2010; Buse et al, 2010b; Blevins et al, 2011; Buse et al, 2011; Taylor et al, 2011).

NICE guidance

Current NICE guidance remains largely unchanged over the past 3 years. A guideline including exenatide twice daily, sitagliptin and vildagliptin was released shortly after the first version of this article was published (NICE, 2009). This includes an algorithm for blood glucose-lowering therapy in people with type 2 diabetes, which was reproduced in the previous CPD module. The guideline has been supplemented by technology appraisals for newer GLP-1 receptor agonists (NICE, 2010; 2012). This helpful structure enables clinicians to make prescribing decisions with patients based on the characteristics of the agents themselves as well as taking into account the challenges and aspirations of each individual. The guideline is currently undergoing revision.

Relevant documents for Scotland have been produced by the Scottish Intercollegiate Guidelines Network and the Scottish Medicines Consortium (some Welsh documentation also exists). The scope of these, and the NICE documents, in terms of therapies covered, is summarised in *Table 4*.

Page points

1. Four DPP-4 inhibitors are currently available for use in clinical practice in the UK – sitagliptin, vildagliptin, saxagliptin and linagliptin.
2. Recent developments have seen extensions of licensed use in various levels of renal impairment. Whether there is a need to reduce drug dosage or perform additional monitoring with declining renal function depends on the route of elimination of the agent, and there are differences within the class in this regard.
3. There is now an extensive range of glucose-lowering agents available for use in daily diabetes practice. Ideally decisions should be based on a balance between efficacy, utility and adverse effects.
4. Current NICE guidance remains largely unchanged over the past 3 years. A guideline including exenatide twice daily, sitagliptin and vildagliptin was released shortly after the first version of this article was published.

Table 3. Goals and methods of some head-to-head incretin clinical trials (adapted with permission from Reid, 2012; list of trials not exhaustive).

	Exenatide versus liraglutide (LEAD-6) (Buse et al, 2009)	Exenatide versus liraglutide (LEAD-6 extension) (Buse et al, 2010a)	Exenatide versus sitagliptin (DeFronzo et al, 2008)	Liraglutide versus sitagliptin (1860-LIRA-DPP-4 and extension) (Pratley et al, 2010; 2011)	Exenatide versus sitagliptin (Arnolds et al, 2010)	Sitagliptin versus saxagliptin (Scheen et al, 2010)
Primary endpoint	Change in HbA_{1c} from baseline to week 26	Change in HbA_{1c} from week 26 to week 40	Change in FPG and PPG over 2 weeks	Change in HbA_{1c} from baseline to week 26, then to week 52	Unadjusted 6-hour PPG excursion at 4 weeks	Change in HbA_{1c} from baseline to week 18
Design	26-week, randomised, open-label, active-comparator, parallel-group, multinational	14-week extension	5-week, randomised, double-blind, crossover, multicentre	26-week, randomised, open-label, active-comparator, parallel-group, multinational; extension phase to 52 weeks	4-week, single-centre, randomised, open-label, active comparator, 3-arm parallel-group	18-week, multicentre, randomised, double-blind, non-inferiority
Patients	464	389	61	665	48	801
Age (years)	18–80	–	18–70	18–80	35–70	≥18
Baseline HbA_{1c} (mmol/mol [%])	53–97 (7.0–11.0)	–	53–97 (7.0–11.0)	58–86 (7.5–10.0)	53–86 (7.0–10.0)	48–86 (6.5–10.0)
Baseline BMI (kg/m^2)	≤45	–	25–45	≤45	21.0–39.9	–
Baseline treatment	Stable, maximally tolerated doses of metformin, SU, or both for at least 3 months	Stable, maximally tolerated doses of metformin, SU, or both for at least 3 months	Stable treatment with metformin	Stable treatment with metformin ≥1500 mg/day for at least 3 months	Stable treatment with metformin with or without SU or insulin glargine/detemir/NPH with or without stable dose of metformin for at least 3 months	Stable treatment with metformin 1500–3000 mg/day for at least 8 weeks
Treatment	Baseline treatment (SU could be reduced up to 50%) plus: • Exenatide 5 µg BD × 4 weeks, then 10 µg BD × 22 weeks ***or*** • Liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 1 week, then 1.8 mg QD × 24 weeks	Baseline treatment (SU could be reduced up to 50%) plus: • Exenatide-treated patients switched to liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 1 week, then 1.8 mg QD × 12 weeks ***or*** • Liraglutide-treated patients continued	• Exenatide 5 µg BD × 1 week, then 10 µg BD × 1 week ***or*** • Sitagliptin 100 mg QAM × 2 weeks	• Liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 25 weeks ***or*** • Liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 1 week, then 1.8 mg QD × 24 weeks ***or*** • Sitagliptin 100 mg/day • Same treatment continued to week 52	• Baseline SU was discontinued • Insulin treatment switched to insulin glargine to achieve FPG ≤100 mg/dL • Exenatide 5 µg BD × 2 weeks, then 10 µg BD × 2 weeks ***or*** • Sitagliptin 100 mg QD ***or*** • Metformin + insulin glargine	• Sitagliptin 100 mg QD ***or*** • Saxagliptin 5 mg QD

1860-LIRA-DPP-4=1860-Liraglutide-Dipeptidyl Peptidase-4 trial; BD=twice daily; BMI=body mass index; FPG=fasting plasma glucose; LEAD-6=Liraglutide Effect and Action in Diabetes-6 trial; NPH=neutral protamine Hagedorn; PPG=postprandial plasma glucose; QAM=every morning; QD=once daily; SU=sulphonylurea.

Cost savings

In austere times, however, the UK government has introduced QIPP (Quality, Innovation, Productivity and Prevention; Department of Health, 2011) savings within the NHS in England in a very short timeframe. Other nations have their own equivalents.

QIPP is a large-scale transformational programme for the NHS, involving staff, clinicians, patients and the voluntary sector. It is intended to improve the quality of care the NHS delivers while making up to £20 billion of efficiency savings by 2014–15. This has brought the cost of agents into sharp focus. In diabetes, the focus has included shifting away from analogue to human insulin usage in type 2 diabetes (National Prescribing Centre, 2012). In addition, the author has noticed that some primary care trusts have been insisting that high percentages of patients taking combinations of oral hypoglycaemic agents should be on sulphonylureas and metformin. The intention is to restrict access to more expensive newer drugs. Against this has to be balanced the recent European driving directive that disqualifies drivers for a year if they experience two or more hypoglycaemic episodes requiring third-party intervention (Drivers Medical Group, 2011). The tensions between political, economic and statutory requirements make individual prescribing decisions even more complex and threaten to undermine the trusting relationship between clinicians and the people they care for.

Future glucose-lowering agents

Sodium–glucose co-transporter 2 (SGLT2) inhibitors are under active development by several pharmaceutical companies. These agents block the action of SGLT2 in reabsorbing glucose and sodium from the renal tubules resulting in significant urinary glucose excretion, reduction in blood glucose and weight loss. Significant glucose lowering was observed in phase III

Table 4. Coverage of GLP-1 receptor agonists and DPP-4 inhibitors in therapy area guidelines and technology appraisals in the UK.

Agent	AWMSG (see specific references)	NICE (see specific references)	SIGN (see specific references)	SMC (SMC, 2012)
DPP-4 inhibitors				
Sitagliptin (including in fixed-dose combination)	–*	CG87 (NICE, 2009)	SIGN 116 (SIGN, 2010)	408/07, 492/08, 505/08, 607/10 and 627/10,
Vildagliptin (including in fixed-dose combination)	–*	CG87 (NICE, 2009)	SIGN 116 (SIGN, 2010)	435/07, 477/08 and 571/09
Saxagliptin	Advice No 2011 (AWMSG, 2011)	–†	SIGN 116 (SIGN, 2010)	603/10
Linagliptin	*Final Appraisal Recommendation not yet available*	–†	–†	746/11
GLP-1 receptor agonists				
Exenatide twice daily	–*	CG87 (NICE, 2009)	SIGN 116 (SIGN, 2010)	376/07 and 684/11
Liraglutide	–*	TA203 (NICE, 2010)	SIGN 116 (SIGN, 2010)	585/09
Exenatide once weekly	–*	TA248 (NICE, 2012)	–†	748/11

AWMSG=All Wales Medicines Strategy Group; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; NICE=National Institute for Health and Clinical Excellence; SIGN= Scottish Intercollegiate Guidelines Network; SMC=Scottish Medicines Consortium.

*Not appraised as covered by NICE.
†Document publication pre-dated drug availability.

Page points

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2. QIPP is a large-scale transformational programme for the NHS, involving staff, clinicians, patients and the voluntary sector. It is intended to improve the quality of care the NHS delivers while making up to £20 billion of efficiency savings by 2014–15.
3. The tensions between political, economic and statutory requirements make individual prescribing decisions even more complex and threaten to undermine the trusting relationship between clinicians and the people they care for.

Box 1. Case example.

Narrative

Paul is a 55-year-old delivery driver who has had type 2 diabetes for 10 years. He is recently divorced and has two children aged 23 and 19. His father and one uncle developed type 2 diabetes in their 70s, while his sister had gestational diabetes in two of her three pregnancies. There is no family history of heart disease.

For the first 2 years after his diagnosis he managed his diabetes by diet alone. He was then put on metformin monotherapy for a further 2 years and is now taking metformin 1 g three times daily and gliclazide 160 mg twice daily. His other medication includes ramipril 5 mg once-daily and simvastatin 40 mg at night. He has no problem with self-monitoring of his blood glucose but has not thought seriously about injecting himself as part of his treatment. He takes little exercise and admits to eating a lot of convenience food

His HbA_{1c} level is 68 mmol/mol (8.4%). His body mass index is 35 kg/m^2. His lipid profile is as follows: total cholesterol level, 4.0 mmol/L; triglyceride level, 1.6 mmol/L; HDL-cholesterol level, 1.0 mmol/L; LDL-cholesterol level, 1.8 mmol/L. His blood pressure is 138/78 mmHg. He has normal renal function. Paul's weight has increased by 6 kg since being on the highest dose of sulphonylurea, which has made him quite despondent. He feels self-conscious about his appearance, especially as he has just started on a new relationship. He has no significant microvascular complications.

Discussion

Paul is typical of many people whose glycaemic control is complicated by weight gain as a result of excessive calorific intake, sedentary lifestyle and treatment with some oral blood glucose-lowering agents. He is now living separately from his ex-wife and drives for a living. He has been fortunate so far not to have incurred significant macrovascular or microvascular complications.

While lifestyle changes, including appropriate dietary advice and exercise, are central to any strategy intended to help both his hyperglycaemia and his weight gain, other measures may be required. Insulin would help lower his HbA_{1c} closer to target but could result in weight gain or hypoglycaemia. The latter might prove very problematic in respect of his occupation. Pioglitazone can lower blood glucose but can result in weight gain as well.

If he was reluctant to inject it would be worthwhile starting him on a DPP-4 inhibitor. These oral agents can be effective glucose-lowering drugs, without the disadvantage of weight gain and significant hypoglycaemia.

If losing weight, as well as improving glycaemic control, was his priority, and he did not mind injecting once or twice daily, he might well benefit from treatment with liraglutide or exenatide. He might also consider exenatide once weekly if reduced frequency of injection was a priority. A close eye would need to be kept on his blood glucose levels during the initial phase in case hypoglycaemia occured – in which case his dose of sulphonlyurea could be halved or even stopped if necessary. (Appropriate adjustment of the regimen also applies regarding DPP-4 inhibitors.) He should be counselled about the possibility of some nausea early on in GLP-1 receptor agonist therapy. He should also be advised to stop his GLP-1 receptor agonist immediately if abdominal or back pain develops and to seek expert advice directly.

trials (Ferrannini et al, 2010). The main side effects are an increase in genital infections (such as candidiasis and occasional urinary tract infection). Dapagliflozin is the first in the SGLT2 class to apply for licensing (Tahrani and Barnett, 2010). Others to follow include canagliflozin, empagliflozin, ipragliflozin and tofogliflozin.

A number of glucokinase activators are undergoing pre-licensing trials. These agents act by promoting intracellular phosphorylation of glucose, which, in turn, mediates cell membrane depolarisation, calcium influx and release of insulin from insulin granules (Matschinsky et al, 2011). Increased understanding of glucagon's role in enhancing hepatic glucose output in type 2 diabetes has highlighted the glucose-lowering potential of glucagon receptor antagonists (Bagger et al, 2011). Several are in advanced stages of development.

Over-expression of sirtuin deacetylase receptors by resveratrol, found in the skin of red grapes, results in normalisation of blood glucose and weight loss in rodents (Imai and Guarente, 2010). Concentrated forms of resveratrol are being trialled in humans.

The link between bowel flora, microbiota, and glucose handling has been explored for its therapeutic possibilities (Kootte et al, 2012). Alterations in the constitution of bowel bacteria have been observed in patients with both type 1 and type 2 diabetes. Intraluminal secretion of lipopolysaccharides leads to activation of GPRs, enhanced GLP-1 release and reductions in blood glucose (Ahrén, 2009). GPR 119 and GPR 40 agonists are being actively studied.

Conclusion

As experience grows with newer agents, their use is likely to increase. Existing agents have their limitations but have the advantage of long-term use. As with any drug, new or old, constant surveillance is needed if rare long-term complications associated with their use are to be detected. Nevertheless, the continuing interest of researchers and pharmaceutical companies in elucidating the mechanisms underlying diabetes and developing better treatments is essential if the lives of those with diabetes are to be constantly improved. ■

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"The continuing interest of researchers and pharmaceutical companies in elucidating the mechanisms underlying diabetes and developing better treatments is essential if the lives of those with diabetes are to be constantly improved."

CPD module

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 new 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. **According to experimental studies, which is the single most appropriate statement regarding the effect of incretin hormones on glucose-dependent insulin secretion? Select ONE option only.**
   A. A decreased insulin response is observed with oral glucose.
   B. A decreased insulin response is observed with parenteral glucose.
   C. An enhanced insulin response is observed with oral glucose.
   D. An enhanced insulin response is observed with parenteral glucose.
   E. None of the above.

2. **In type 2 diabetes, which is the single most appropriate statement regarding beta-cell sensitivity? Select ONE option only.**
   A. The beta-cell response to glucose-dependent insulinotropic polypeptide (GIP) is increased.
   B. The beta-cell response to GIP is slightly reduced.
   C. The beta-cell response to GIP is largely lost.
   D. The beta-cell response to glucagon-like peptide-1 (GLP-1) is increased.
   E. The beta-cell response to GLP-1 is largely lost.

3. **Which one of the following anatomical parts of the gastrointestinal system would be the most likely site of GLP-1 secretion? Select ONE option only.**
   A. Stomach
   B. Duodenum
   C. Jejunum
   D. Ileum
   E. Colon

4. **Which one of the following is not a recognised response to GLP-1? Select ONE option only.**
   A. Increased insulin secretion.
   B. Increased gastric emptying.
   C. Induced satiety.
   D. Reduced food intake.
   E. Suppressed glucagon secretion.

5. **Which is the single most appropriate estimation of the time it takes the gut to inactivate human GLP-1? Select ONE option only.**
   A. 1 minute.
   B. 10 minutes.
   C. 20 minutes.
   D. 10 hours.
   E. 1 hour.

6. **Which one of the following blood glucose-lowering therapies works as a GLP-1 receptor agonist? Select ONE option only.**
   A. Dapagliflozin
   B. Insulin detemir
   C. Saxagliptin
   D. Liraglutide
   E. Repaglinide

7. **A 57-year-old man has renal impairment and type 2 diabetes. His glycaemic control is poor despite taking gliclazide 160 mg twice daily and he absolutely declines any consideration of treatments that involve injections. His results are:**
   - **Urine ketones: negative**
   - **Urine glucose: ++++**
   - **Random blood glucose: 15 mmol/L**
   - **HbA_{1c}: 86 mmol/mol**
   - **CrCl: 25 mL/min**

   As he is experiencing hypoglycaemic episodes, you choose to discontinue gliclazide. Which one of the following is the most appropriate alternative blood glucose-lowering agent? Select ONE option only.
   A. Exenatide twice daily
   B. Liraglutide
   C. Metformin
   D. Rosiglitazone
   E. Linagliptin

8. **A 49-year-old bus driver has type 2 diabetes. His eating habits are erratic, frequently missing breakfast, but his BMI remains 30 kg/m^2 and his HbA_{1c} level is 64 mmol/mol (8%). He takes metformin 1 g twice daily regularly. Aside from lifestyle interventions, among the following, which is the most appropriate next management step? Select ONE option only.**
   A. Add acarbose.
   B. Add insulin glargine.
   C. Add gliclazide.
   D. Add vildagliptin.
   E. Increase metformin.

9. **Which one of the following is a reason given by NICE for which a thiazolidinedione may be preferable to a dipeptidyl peptidase-4 (DPP-4) inhibitor? Select ONE option only.**
   A. Patient preference.
   B. Previous good response to a DPP-4 inhibitor.
   C. When patients are intolerant of sulphonylureas.
   D. When there is a significant risk of hypoglycaemia or its consequences.
   E. Where the individual has marked insulin sensitivity.

10. **A 53-year-old woman has type 2 diabetes, disabling hip osteoarthritis and morbid obesity. She requests treatment that will increase her chances of being considered a safer candidate for hip surgery. Despite regular support, lifestyle advice and metformin 1g twice daily, her HbA_{1c} over the past 2 years has been between 68 and 85 mmol/mol (8.4–9.9%). Aside from a review of lifestyle interventions, which one of the following is the most appropriate next management step? Select ONE option only.**
    A. Exenatide twice daily
    B. Gliclazide
    C. Premixed insulin
    D. Pioglitazone
    E. Sitagliptin