Future glucose-lowering drugs for type 2 diabetes

Clifford J Bailey, Abd A Tahrani, Anthony H Barnett

Summary
The multivariable and progressive natural history of type 2 diabetes limits the effectiveness of available glucose-lowering drugs. Constraints imposed by comorbidities (notably cardiovascular disease and renal impairment) and the need to avoid hypoglycaemia, weight gain, and drug interactions further complicate the treatment process. These challenges have prompted the development of new formulations and delivery methods for existing drugs alongside research into novel pharmacological entities. Advances in incretin-based therapies include a miniature implantable osmotic pump to give continuous delivery of a glucagon-like peptide-1 receptor agonist for 6–12 months and once-weekly tablets of dipeptidyl peptidase-4 inhibitors. Hybrid molecules that combine the properties of selected incretins and other peptides are at early stages of development, and proof of concept has been shown for small non-peptide molecules to activate glucagon-like peptide-1 receptors. Additional sodium-glucose co-transporter inhibitors are progressing in development as well as possible new insulin-releasing biological agents and small-molecule inhibitors of glucagon action. Adiponectin receptor agonists, selective peroxisome proliferator-activated receptor modulators, cellular glucocorticoid inhibitors, and analogues of fibroblast growth factor 21 are being considered as potential new approaches to glucose lowering. Compounds that can enhance insulin receptor and post-receptor signalling cascades or directly promote selected pathways of glucose metabolism have suggested opportunities for future treatments. However, pharmacological interventions that are able to restore normal β-cell function and β-cell mass, normalise insulin action, and fully correct glucose homeostasis are a distant vision.

Introduction
A wealth of evidence from prospective and retrospective clinical studies supports the premise that early, effective, and sustained glycemic control defers the onset of diabetes and reduces the severity of associated complications.1–4 However, more than a third of all patients with diabetes do not achieve or maintain an appropriate glycemic target.1,4 Although this situation is attributed partly to late diagnosis of diabetes, delayed introduction or insufficient escalation of treatment, or poor patient adherence, more efficacious and durable treatments are needed. Type 2 diabetes is usually the product of various genetic susceptibilities and environmental factors that interact to create a highly heterogeneous and progressive pathological changes against which existing treatments have substantial limitations.5 About half of all patients with type 2 diabetes require combinations of two or more differently acting non-insulin glucose-lowering drugs and about a third of patients will require insulin.6 Moreover, the complications and comorbidities (eg, cardiovascular disease and renal impairment) that typically accompany advanced states of insulin resistance and pancreatic β-cell dysfunction restrict the choice of available treatments.

This update of a previous narrative Review in The Lancet in 20117 uses the same literature search procedure to carry the review forward to June, 2015. Emphasis is given to clinical studies of agents that are advanced in development and preclinical experimentation that explores potential new therapeutic mechanisms for diabetes. The main sites of action of present and possible future glucose-lowering treatments are summarised in figure 1 and key features of the modes of action of potential future therapies are summarised in table 1.

Pancreatic β-cell function

Overview
Interventions with lasting efficacy are needed to prevent and reverse the progressive reduction in pancreatic β-cell function and β-cell mass in patients with type 2 diabetes.9 Compounds acting at the level of the β cell currently under investigation include the small molecule insulin releasers, glucokinase activators, fatty acid receptor agonists, and imeglimin.

Small molecule insulin releasers
In addition to established initiators of insulin secretion (sulfonylureas and meglitinides), many compounds are known to improve β-cell function in vitro. These small molecule insulin releasers include succinate esters, imidazolines, selective phosphodiesterase inhibitors, α-2 adrenergic antagonists, and agents that close Kir6.2 potassium channels or open membrane calcium channels. However, the in-vivo effects of most of these compounds are too generalised to specifically target β cells and few have progressed in development.10

Glucokinase activators
Activators of the glucose phosphorylating enzyme, glucokinase, increase both insulin secretion and hepatic glucose metabolism (figure 2). Phase 2 and phase 3 studies in patients with type 2 diabetes have shown modest glucose-lowering for 4–6 months, but efficacy quickly reduces thereafter.9 With stimulation of insulin secretion at low glucose concentrations, glucokinase activators are prone to cause hypoglycaemia. However, glucokinase is regulated differently in the liver to the β cell, and attention is now focused on the development of liver-selective glucokinase activators. Accumulation of hepatic triglycerides often occurs during protracted
**Review**

GPR119 agonists activate adenylate cyclase, increasing cyclic adenosine monophosphate and potentiating nutrient-induced insulin secretion in a similar manner to glucagon-like peptide-1 (GLP1). Both GPR40 and GPR119 are expressed by enterodocrine pancreatic cells and other cells, K cells, L cells, and I cells, and synthetic agonists for these receptors can increase the secretion of glucose-dependent insulinoetropic peptide (also known as gastric inhibitory polypeptide, GIP), GLP1, peptide YY (PYY), and cholecystokinin, potentially enhancing the incretin and satiety effects of these hormones. GPR40 and GPR119 receptors are also expressed by pancreatic α cells and agonists might increase glucagon secretion.

Another long-chain fatty acid receptor, GPR120 (also known as FFAR4), expressed mainly by adipose tissue, promotes adipogenesis. Small molecule agonists of this receptor improve glucose homeostasis by increasing insulin sensitivity and reducing ectopic fat in preclinical studies.

**Imeglimin**

Imeglimin is a triazine derivative that enhances glucose-induced insulin secretion, especially the first phase, and improved glycaemic control during phase 2 studies in type 2 diabetes. It seems to change cellular energetics, in part through closure of mitochondrial permeability transition pores, which can also improve peripheral insulin sensitivity and reduce hepatic gluconeogenesis.

**Incretin-based therapies**

**Overview**

Hormonal signals from the alimentary tract continue to provide important therapeutic templates for type 2 diabetes. The main incretin hormone, GLP1, has been successfully exploited in this respect by changing the molecule to avoid rapid inactivation by the enzyme dipeptidyl-peptidase-4 (DPP4) or by inhibiting DPP4.

**GLP1 receptor agonists**

Injectable GLP1 receptor agonists (exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide) potentiate nutrient-induced insulin release, suppress excess glucagon secretion, delay gastric emptying, and exert satiety effects that assist with weight control. Although these agents have increased β-cell mass in animal studies, this finding has yet to be clearly shown in human beings with type 2 diabetes. To avoid daily or weekly injections, a matchstick-sized subcutaneously implanted miniature osmotic pump has been developed for continuous delivery of up to 80 μg/day of exenatide. In an extended phase 2 study, implants delivering doses of 40 μg/day or more of this GLP1 receptor agonist for 48 weeks in patients with type 2 diabetes reduced HbA₁c by 0.93–1.42%; 10–15 mmol/mol) from a baseline of about 8% (64 mmol/mol) and weight (by 3.0–4.2 kg) from a baseline of 93 kg. Initial dose-related nausea

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**Figure 1: Intervention sites for glucose-lowering, showing available treatments and possible new treatments**

- **Available treatments**
  - α-glucosidase inhibitors
  - Slow carbohydrate digestion
  - Colesevelam®
  - Bile sequestrant
  - Pramlintide
  - Amylin analogue
  - Bromocriptine®
  - Dopamine D2 agonist
  - GLP-1 receptor agonists
  - Enhance incretin effect
  - DPP4 inhibitors
  - Enhance incretin effect
  - Sulfonylureas
  - Stimulate insulin secretion
  - Meglitinides
  - Stimulate insulin secretion
  - Metformin
  - Reduce glucose production, increase glucose use, counter insulin resistance
  - Insulin injections, pumps, inhalers
  - Insulin resistance increase glucose use, counter insulin resistance
  - Reduce glucose production, insulin resistance
  - Increase glucose uptake, storage, and metabolism, suppress glucose production, decrease lipolysis
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  - DPP4 inhibitors
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  - SGLT1 inhibitors
  - Delay glucose absorption
  - Satiety-inducing agents
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  - DPP4 inhibitors
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  - GLP1 receptor agonists
  - Enhance insulin secretion
  - Inhibitors of glucagon secretion and glucagon action
  - Suppress counter-regulation
  - Direct inhibitors of hepatic glucose production and stimulants of muscle glucose uptake and metabolism
  - Enhance insulin secretion
  - Small molecule insulin mimetics
  - Enhance insulin action
  - Adipokine analogues agonists/ inhibitors, FGF21 analogues, SPPARMs, 11βHSD1 inhibitors
  - Variously counter insulin resistance
  - Small molecule insulin mimetics
  - Enhance insulin action
  - Novel insulin analogues, formulations and delivery routes—oral, buccal, skin—smart insulins
  - Enhance insulin action
  - Further SGLT2 inhibitors
  - Glucosuric

- **Possible future treatments**
  - SGLT2 inhibitors
  - Glucosuric
  - Novel insulin analogues, formulations and delivery routes—oral, buccal, skin—smart insulins
  - Enhance insulin action
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**Table 1:** Glucose-lowering treatments and possible new treatments

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<td>Reduce glucose production, insulin resistance</td>
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**Figure 1:** Intervention sites for glucose-lowering, showing available treatments and possible new treatments. GPR119 agonists activate adenylate cyclase, increasing cyclic adenosine monophosphate and potentiating nutrient-induced insulin secretion in a similar manner to glucagon-like peptide-1 (GLP1). Both GPR40 and GPR119 are expressed by enterodocrine pancreatic cells and other cells, K cells, L cells, and I cells, and synthetic agonists for these receptors can increase the secretion of glucose-dependent insulinoetropic peptide (also known as gastric inhibitory polypeptide, GIP), GLP1, peptide YY (PYY), and cholecystokinin, potentially enhancing the incretin and satiety effects of these hormones. GPR40 and GPR119 receptors are also expressed by pancreatic α cells and agonists might increase glucagon secretion.

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(mostly transient) was reported by about a third of participants and antibodies were detected in up to 10% of patients but did not seem to impair efficacy of exenatide.20

This therapy is in phase 3 of development.

Another approach to avoid injections is an oral tablet formulation of the GLP1 receptor agonist semaglutide. This peptide is in phase 3 trials, including one already completed trial (NCT02054897), as a once-weekly subcutaneous injection. The oral formulation is suggested to be equally effective.21 Studies in mice have shown that GLP1 receptor agonists can also be delivered by bioencapsulation in chloroplasts.22 Several non-peptide small molecule GLP1 receptor agonists have been characterised in preclinical studies, but clinical efficacy has yet to be reported.23

Dipeptidyl-peptidase-4 inhibitors

DPP4 inhibitors (eg, sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin) are once-daily (or twice-daily for vildagliptin) oral drugs that enhance the effects of

<table>
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<tr>
<th>Mechanism of action</th>
<th>Glucose-lowering effect</th>
<th>Development status</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Glucokinase activators</td>
<td>Increase glucokinase activity in pancreatic islets and liver</td>
<td>Increase insulin secretion and hepatic glucose uptake</td>
<td>Phase 3</td>
</tr>
<tr>
<td>GLP4 (also known as FFAR4) and GLP11 agonists</td>
<td>Activates fatty acid receptors in pancreatic islets and gut</td>
<td>Increase insulin secretion and enteroendocrine L-cell incretin secretion</td>
<td>Phase 1–3</td>
</tr>
<tr>
<td>Imeglimin</td>
<td>Close mitochondrial transition pores</td>
<td>Increases insulin secretion and decreases gluconeogenesis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Exenatide implantable osmotic pump</td>
<td>GLP1 receptor agonist</td>
<td>Mimes effects of GLP1</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Oral and subcutaneous semaglutide</td>
<td>GLP1 receptor agonist</td>
<td>Mimics effects of GLP1</td>
<td>Phase 2–3</td>
</tr>
<tr>
<td>Non-peptide GLP1 receptor agonists</td>
<td>GLP1 receptor agonist</td>
<td>Mimics effects of GLP1</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Omasglinatin (once-weekly)</td>
<td>DPP4 inhibitor</td>
<td>Increase endogenous incretin action</td>
<td>Phase 3</td>
</tr>
<tr>
<td>TGRS (also known as GPBAR1) agonists</td>
<td>Stimulate bile acid receptors in ileum</td>
<td>Increase L-cell incretin secretion</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Fixed-ratio combinations; GLP1 receptor agonists with insulin</td>
<td>GLP1 receptor agonist and basal insulin</td>
<td>Mimics effects of GLP1 and insulin at same time</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Hybrid and chimeric designer peptides</td>
<td>Agonism or partial antagonism of selected peptides</td>
<td>Mimics effects of selected incretins and other peptides</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Glucagon receptor antagonists</td>
<td>Decrease glucagon action</td>
<td>Decrease hepatic glucose output</td>
<td>Preclinical to phase 2</td>
</tr>
<tr>
<td>Insulin receptor signalling potentiators</td>
<td>Prolong Tyr phosphorylation of insulin receptor B-subunit</td>
<td>Increase insulin action</td>
<td>Preclinical</td>
</tr>
<tr>
<td>SGLT1 and 2 inhibitors</td>
<td>Selectively decrease SGLT1 (also known as SLC5A1) and SGLT2 (also known as SLC5A2) activity in gut and kidney</td>
<td>Increase renal glucose elimination; delays gut glucose absorption; changes incretin secretion</td>
<td>Phase 2–3</td>
</tr>
<tr>
<td>Non-peptide adiponectin receptor agonists</td>
<td>Adiponectin R1/R2 agonists</td>
<td>Increase insulin action</td>
<td>Preclinical</td>
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<tr>
<td>FGF21 analogues</td>
<td>FGF21 receptor agonists</td>
<td>Increase insulin sensitivity and improves lipid profile</td>
<td>Phase 1</td>
</tr>
<tr>
<td>GPR120 (also known as FFAR4)</td>
<td>Activates fatty acid receptors in adipose and other tissues</td>
<td>Increases insulin sensitivity and adipogenesis</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Selective peroxisome proliferator-activated receptor modulators</td>
<td>Selective peroxisome proliferator-activated receptor alpha, gamma, and delta agonists</td>
<td>Increase insulin sensitivity, adipogenesis or lipid profile, and slet β-cell viability</td>
<td>Phase 1–2</td>
</tr>
<tr>
<td>11β-hydroxysteroid dehydrogenase-1 inhibitors</td>
<td>Inhibit 11β-hydroxysteroid dehydrogenase-1 conversion of cortisone to cortisol in liver and adipose tissue</td>
<td>Increase insulin sensitivity and improves lipid profile</td>
<td>Phase 1–2</td>
</tr>
<tr>
<td>Fructose-1,6 bisphosphatase inhibitors</td>
<td>Increase fructose-1,6 bisphosphatase activity</td>
<td>Decrease hepatic glucose output</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Adenosine monophosphate kinase activators</td>
<td>Increase adenosine monophosphate kinase cellular effects on nutrient metabolism</td>
<td>Increase glucose uptake and metabolism</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

This list is not comprehensive but shows the various mechanisms and stages of development represented in this Review.

Table 1: List of some potential new glucose-lowering medications for type 2 diabetes
endogenous incretins by prolonging their circulating half-lives. Because the side-effects of these drugs have been minimal to-date, long-acting DPP4 inhibitors have been investigated. In the most advanced stage of development, omaglitogliptin has shown similar efficacy and tolerability as sitagliptin in phase 3 clinical studies.

TGR5 agonists
The bile acid sequestrant colesvelam, which is indicated for use as a glucose-lowering drug in some countries, raises the possibility that carriage of bile acids more distally along the ileum could activate the TGR5 (also known as GPBAR1) bile acid receptors on L cells and enhance GLP1 secretion. Preliminary studies are investigating whether poorly absorbed TGR5 agonists can act distally along the intestinal tract to enhance GLP1 secretion.

Peptide combinations
A mix of two differently acting peptides in the same injection became a therapeutic reality with the introduction of IDegLira, a fixed-ratio combination of liraglutide with insulin degludec (ratio of 1-8 mg of liraglutide to 50 units of insulin degludec). This combination is titrated in a similar manner to insulin, and during a 1-year prospective randomised phase 3 trial in patients who had insulin-naive type 2 diabetes, once-daily subcutaneous injection of IDegLira reduced HbA₁c by 1-84% (20-2 mmol/mol) compared with 1-40% (15-3 mmol/mol) for insulin degludec alone and 1-21% (13-2 mmol/mol) for liraglutide alone (each p<0.0001 versus IDegLira). The combination achieved this effect with a lower insulin dose (39 units) than insulin degludec alone (62 units; p<0.0001), and avoided weight gain in patients (p<0.0001 between each treatment group). Preliminary data from a phase 2 study indicate that a fixed-ratio combination of lixisenatide and insulin glargine (Lixilan: ratio 50 μg of lixisenatide to 100 units of glargine) has similar efficacy in patients who had insulin-naive type 2 diabetes.

Preclinical and clinical studies have also explored the use of hybrid peptides in which two or more peptides are linked together to form a single molecule. These hybrids have mostly included combinations of GLP1 with glucagon, GIP, or other intestinal peptides. Hybrid molecules provide an opportunity to combine the effects of various peptides that affect blood glucose, lipids, satiety, energy expenditure, and adiposity, such as incretins, glucagon receptor agonists or antagonists, oxyntomodulin, PYY, obestatin, and ghrelin antagonists. These agents can be customised with a selection of desired sequences to construct chimeric molecules that exploit particular epitopes and enable new therapeutic portfolios in a single molecule. For example, molecules with satiety-inducing, weight-lowering, and glucose-lowering properties might reproduce the metabolic effects of bariatric surgery. Although substantial physicochemical constraints and potential immunological issues need to be addressed, multipurpose designer molecules offer a novel potential therapeutic prospect.

Glucagon secretion and action
Reduction of prandial (but not fasting) glucagon secretion by pancreatic α cells is an important action of GLP1 receptor agonists. Other inhibitors of glucagon secretion (eg, somatostatin analogues) have not been suitable for glucose-lowering in type 2 diabetes, mainly because of interference with the counter-regulatory response to hypoglycaemia, which is already defective in most patients.

Despite many accounts in the medical literature of glucagon receptor antagonists over more than 20 years, few have progressed beyond initial clinical trials. Unwanted effects on liver function have been described with some glucagon receptor antagonists, and glucagon receptor antagonism could possibly cause compensatory hyperglucagonaemia and rebound hyperglycaemia if treatment is not maintained.

Insulin action
Insulin binds to the extracellular α subunits of the insulin receptor, changing their conformation. This effect in turn changes conformation of the β subunits.
that extend into the cytosol, exposing tyrosine residues in the β subunits. Phosphorylation of these residues enables the β subunits to act as kinase enzymes, activating insulin receptor substrate (IRS) proteins that trigger the various post-receptor pathways responsible for the genomic and non-genomic actions of insulin. Thus, insulin resistance in patients with type 2 diabetes has many potential causes, many different presentations, and many possible sites for intervention.3,5,7–9 However, the rate-limiting defect is almost never identified and the potential benefits gained by circumventing any one defect might be offset by disturbances elsewhere in the insulin-receptor–effector pathways. Moreover, the various post-receptor signalling pathways of insulin action interact with, and are partly shared by, many other cellular signalling pathways, creating a challenge for any therapeutic intervention to act selectively on insulin action without interfering with other cellular control processes. In view of these constraints, much research into insulin resistance has, unsurprisingly, not yet yielded a new drug.

Because of the complexity of insulin receptor binding, small (non-peptide) molecules are unlikely to be able to duplicate this act. However, a monoclonal antibody (XmeltA) that exhibits high affinity binding to the insulin receptor at a different site to insulin initiated some of the effects of insulin in animal cells in vitro and improved glycaemic control in insulin resistant diabetic mice.10 This finding suggests that conformational changes to the α subunit of the insulin receptor that differ from those induced by insulin binding could be exploited to produce conformational changes in the β subunit that will elicit therapeutically beneficial effects.

A fungal metabolite, demethylasterriquinone, which interacts directly with the cytosolic part of the insulin receptor β subunit, can initiate IRS-1-mediated post-receptor pathways without needing insulin binding. Although demethylasterriquinone is not suited to clinical development, the metabolite’s ability to control the hyperglycaemia in diabetic animals suggests an opportunity exists for small molecules to mimic the actions of insulin.11

Various drugs have been reported to potentiate insulin-initiated tyrosine phosphorylation of the insulin receptor β subunit, or prevent its tyrosine dephosphorylation by phosphatases.12 In particular, drugs directed against protein tyrosine phosphatase 1B and more general phosphatase inhibitors, such as vanadium salts, have successfully treated hyperglycaemic animals and shown efficacy in clinical trials, but none has proved sufficiently selective or free of side-effects to proceed into routine clinical use.13,41

Several intermediates within or activated by the post-receptor insulin signalling pathways exert a negative feedback by phosphorylating serine residues on the β subunit and IRS proteins (eg, protein kinase C-theta and the mammalian target of rapamycin). Attempts to interrupt this feedback have not been sufficiently selective. Provision of substrates for individual steps in the post-receptor pathways (eg, administration of the chiroinositol analogue pinitol enables signalling through phosphatidylinositol 3-kinase) is another approach under investigation.13

**Sodium-glucose co-transporter inhibitors**

Inhibitors of sodium–glucose co-transporters (eg, canagliflozin, dapagliflozin, and empagliflozin) are mainly directed against SGLT2 (also known as SLC5A2), which is located in the initial part of the proximal tubules and is responsible for reabsorption of about 90% of filtered glucose. Inhibition of SGLT2 causes excess glucose to be eliminated in the urine, which enables insulin-independent lowering of glucose, and lowering of bodyweight and blood pressure.42 Several further SGLT2-selective inhibitors are advanced in development, all offering similar efficacy in clinical trials.43 Sotagliflozin strongly inhibits both SGLT2 and SGLT1 (also known as SLC5A1) and has also shown similar

![Figure 3: Pathways of intracellular insulin signalling showing some of the potential sites for therapeutic intervention](https://example.com/figure3.png)

Figure 3: Pathways of intracellular insulin signalling showing some of the potential sites for therapeutic intervention.

Dotted lines=inhibition. Solid lines=activation. Some agents listed in this figure are not discussed in this update and the reader is referred to references 7 and 8. AKT=protein kinase B. AMPK=adenosine monophosphate-activated protein kinase. eNOS=endothelial nitric oxide synthase. FOXO1=forkhead box protein O1A. GLUT=glucose transporter. IRS=insulin receptor substrate. JNK=c-Jun N-terminal kinase. MAPK=mitogen-activated protein kinase. MEK=mitogen-activated protein kinase. PDCD1=LMP2 death receptor. PPAR=peroxisome proliferator–activated receptor. PI3K=phosphatidylinositol 3-kinase. PIP2=phosphatidylinositol-3,4-bisphosphate. PIP3=phosphatidylinositol-3,4,5-trisphosphate. PKC=protein kinase C. PPARC=peroxisome proliferator–activated receptor. SOCS3=suppressor of cytokine signalling 3. SGLT=glucose transporter. STAT5B=signal transducer and activator of transcription 5B. TNFα=tumour necrosis factor α.
**Adipokine-based treatments**

In addition to facilitating weight loss through centrally mediated satiety and thermogenic effects, leptin exerts direct peripheral effects to improve insulin action and suppress glucagon. However, the glucose-lowering efficacy of leptin and leptin analogues was nominal during phase 3 trials in obese patients with type 2 diabetes, and benefits might only occur in individuals who are severely leptin deficient.6

Concentrations of another adipocyte hormone, adiponectin, are typically low in patients with type 2 diabetes, especially in the overweight, and adiponectin is known to exert several potentially beneficial effects including improved insulin sensitivity, improved endothelial function, and an anti-inflammatory effect.44,45 Orally active small-molecule agonists of the adiponectin receptors, ADIPOR1 and ADIPOR2, have been shown to improve glycaemic control and prolong lifespan in insulin resistant diabetic animals, raising expectations for clinical studies.44,45

Preliminary data suggest that other treatments based on adipocyte hormones could be applied to type 2 diabetes. For example, resistin reduces insulin sensitivity, increases proinflammatory cytokines, and adversely affects vascular function, whereas immunoneutralisation of resistin has improved insulin sensitivity in rodents.46 Increased concentrations of the retinol-binding protein 4 (RBP4), which transports plasma retinoids, have been detected early in the development of insulin resistance, and interventions that reduce RBP4 have increased insulin sensitivity in animals.47

Fibroblast growth factor 21 (FGF21) is a peptide secreted by adipose tissue, liver, and muscle, which promotes fatty acid oxidation and hepatic gluconeogenesis during starvation. Plasma concentrations of FGF21 are raised in obesity and type 2 diabetes, possibly due to FGF21 resistance, and preliminary animal and human studies suggest that administration of FGF21 analogues can improve the lipid profile, reduce insulin resistance, and assist glucose-lowering, partly through increased production of adiponectin.48,49

**Selective peroxisome proliferator-activated receptor modulators**

The nuclear peroxisome proliferator-activated receptor (PPAR) family offers a selection of potentially beneficial therapeutic effects but accompanying side-effects need to be minimised. PPARγ improves insulin sensitivity, glycemic control, and various markers of vascular health while reducing inflammation, but also increases fluid retention and risk of heart failure, reduces bone mineral density, and often causes excessive adipogenesis.46 PPARα improves the lipid profile, reduces inflammation, and seems to benefit microvascular complications, but might raise creatinine and risk of myopathological abnormalities, whereas PPARδ counters weight gain through increased thermogenic energy expenditure, but long-term safety in man is not established.47 Agents that selectively activate PPARγ and PPARα (dual PPARα/γ agonists, or glitazars), and triple PPAR agonists that also activate PPARδ (known as panPPARs) have not been introduced for routine clinical use due to side-effects.48 Attention is directed to more selective PPAR modulators (SPPARMs) designed to capture desired effects and minimise unwanted effects.49 For example, addition of a nonthiazolidinedione SPPARM, INT131, showed similar glucose-lowering efficacy to pioglitazone but with less oedema and less weight gain during a phase 2A, 24-week randomised double-blind study in patients with type 2 diabetes receiving a sulphonylurea with or without metformin.

**Inhibitors of 11β-hydroxysteroid dehydrogenase 1**

Inhibitors of 11β-hydroxysteroid dehydrogenase 1 (11βHSD1) reduce the production of active cortisol from cortisone.45 Such an inhibitor, INCB13739, improved insulin sensitivity, reduced HbA1c by 0-6% (6 mmol/ mol), improved the lipid profile and reduced bodyweight during a 12-week randomised phase 2 double blind placebo controlled study in metformin-treated type 2 diabetes subjects. However, the efficacy achieved with 11βHSD1 inhibitors has been low and although these agents should theoretically restrict cortisol production within the liver and adipose tissue, a reduction of circulating cortisol can occur and cause a compensatory increase in adrenocorticotropic hormone.50

**Agents that directly affect glucose production or metabolism**

Many compounds have been shown to reduce blood glucose in diabetic animals by suppressing hepatic glucose production, but few have progressed in clinical development.46 High risk of hypoglycaemia has been a limitation as noted with glucose-6-phosphatase inhibitors, because these agents inhibit the last step in gluconeogenesis and glycogenolysis. The risk of hypoglycaemia might be lessened with inhibitors of fructose-1,6 bisphosphatase, which create a compensatory increase in glycogenolysis, and some phase 2 clinical studies are in progress.47

Activation of adenosine monophosphate-activated protein kinase (AMPK), which is one of the cellular
mechanisms of metformin and adiponectin, reduces blood glucose by increasing peripheral glucose uptake and increasing the metabolism of glucose and fatty acids. AMP is the main cellular activator of AMPK, and analogues of AMP are being explored as potential treatments.62

Epigenetics, genetics, and proteomics

The epigenetic approach is shown by sirtuins, which are nicotinamide-adenine-dinucleotide-dependent deacetylases and ADP ribosyltransferases that change gene transcription through chromatin silencing. Several small molecule sirtuin activators have produced effects similar to chronic caloric restriction in animal models. These effects include mitochondrial biogenesis and thermogenesis, glucose lowering, and improved vascular function, prompting continuing investigations into potential applications to treat obesity, diabetes, and cardiovascular disease.63,64

Genetic and proteomic studies continue to inform on the multivariable causes and pathogenesis of type 2 diabetes and identify specific treatment targets for a few patients, but for most patients these approaches have yet to inform the design of new drugs.65–67

Antiobesity drugs

Drugs approved for weight loss can assist glycaemic control in overweight and obese patients with type 2 diabetes. These products include the established intestinal lipase inhibitor orlistat and several newly approved satiety-inducing drugs, notably a high dose GLP1 receptor agonist (liraglutide), a 5HT2c serotonin receptor agonist (lorcaserin), a phentermine-topiramate combination, and a bupropion-naltrexone combination.68–70 Further potential inducing drugs, notably a high dose GLP1 receptor agonist lipase inhibitor orlistat and several newly approved satiety-control in overweight and obese patients with type 2 diabetes and identify specific treatment targets for a few patients, but for most patients these approaches have yet to inform the design of new drugs.65–67

Insulins

Advances in insulin treatment for patients with type 2 diabetes are beyond the remit of this Review, and have been reviewed recently.71 Key developments for the immediate future include biosimilar insulins, notably biosimilar glargine and lispro, and the introduction of more concentrated U200–U500 formulations of existing insulins. Clinical assessment of an ultra-fast short-acting formulation of insulin aspart and a long-acting formulation of lispro are advancing in development. An inhaled insulin (afrezza) has received little use since its launch in the USA in 2015: a buccal spray insulin is now available in some countries, and closed-circuit insulin-glucagon pumps and other artificial pancreas devices are advancing in development. Delivery of insulin through skin patches or oral insulin formulations continue to be developed, and so-called smart insulins, which are activated or released from subcutaneous or circulating depots or skin patches in response to rising glucose concentrations, are giving encouraging results in preclinical studies.72

Safety issues

Safety is particularly relevant yet difficult to assess for glucose-lowering treatments in view of their long-term use in patients with comorbidities.73 Cardiovascular risk is substantially raised in patients with type 2 diabetes and the US Food and Drug Administration (FDA) requires a meta-analysis of all cardiovascular events in phase 2 and 3 trials as part of any application for a new glucose-lowering treatment.74–76 The FDA has also requested or encouraged extensive post-marketing randomised controlled cardiovascular safety studies with composite endpoints that include cardiovascular deaths and non-fatal myocardial infarction and stroke (Table 2). The studies completed so far with saxagliptin (SAVOR-TIMI),77 alogliptin (EXAMINE),78 sitagliptin (TECOS),79 and lixisenatide (ELIXA)80 have reassuringly confirmed no adverse composite cardiovascular outcomes, and empagliflozin (EMPA-REG)80 has reported a significant 14% reduction in its composite cardiovascular outcome.80 During these studies other safety issues were being monitored including acute pancreatitis, bone fractures, infections, and cancers, and no significant increases in these adverse events have been reported to date. Although future drugs will ideally give positive outcomes in long-term cardiovascular safety trials, outcomes will vary with the numbers of different cardiovascular diseases, the duration of the study, and other variables across the different trial populations studied. Thus, the question arises as to whether heavy investment into large post-marketing cardiovascular outcome studies for new diabetes drugs could be compromising endeavours in innovative research.

Table 2: Post-marketing randomised cardiovascular safety studies for glucose-lowering drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Start date</th>
<th>End date</th>
<th>Mean or median duration (years)</th>
<th>n Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMINE* Alogliptin</td>
<td>2009</td>
<td>2014</td>
<td>1.5</td>
<td>5380</td>
</tr>
<tr>
<td>SAVOR- TIMI 53* Saxagliptin</td>
<td>2010</td>
<td>2014</td>
<td>2.1</td>
<td>16 492</td>
</tr>
<tr>
<td>TECOS* Sitagliptin</td>
<td>2008</td>
<td>2015</td>
<td>2.8</td>
<td>14 671</td>
</tr>
<tr>
<td>ELIXA* Lixisenatide</td>
<td>2010</td>
<td>2015</td>
<td>~4.0</td>
<td>6075</td>
</tr>
<tr>
<td>EMPA-REG* Empagliflozin</td>
<td>2010</td>
<td>2015</td>
<td>3.1</td>
<td>7020</td>
</tr>
<tr>
<td>LEADER Liraglutide</td>
<td>2010</td>
<td>2016</td>
<td>~5.0</td>
<td>9340</td>
</tr>
<tr>
<td>CANNAS Canagliflozin</td>
<td>2009</td>
<td>2017</td>
<td>~4.0</td>
<td>4407</td>
</tr>
<tr>
<td>EXSCEL Exenatide QW</td>
<td>2010</td>
<td>2018</td>
<td>~5.5</td>
<td>14 000</td>
</tr>
<tr>
<td>CAROLINA Linagliptin</td>
<td>2010</td>
<td>2018</td>
<td>~8.0</td>
<td>6000</td>
</tr>
<tr>
<td>CARMELENA Linagliptin</td>
<td>2013</td>
<td>2018</td>
<td>~8.0</td>
<td>8300</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 Dapagliflozin</td>
<td>2013</td>
<td>2019</td>
<td>~6.0</td>
<td>17 150</td>
</tr>
<tr>
<td>REWIND Dulaglutide</td>
<td>2011</td>
<td>2019</td>
<td>~6.5</td>
<td>9 960</td>
</tr>
<tr>
<td>ACE Acarbose</td>
<td>2009</td>
<td>2017</td>
<td>~4.0</td>
<td>~7 000</td>
</tr>
</tbody>
</table>

MACE=major adverse cardiovascular event. 3 point MACE=composite of cardiovascular death and non-fatal myocardial infarction and stroke. 4 point MACE=3 point MACE plus hospitalisation for another specified cardiovascular event (eg, angina, heart failure). *Studies for which results have already been reported.

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lesions of type 2 diabetes remain elusive. Entirely new existing drugs or new members of existing classes with advanced in development are different formulations of adiponectin receptor agonists, and AMPK activators. activate GLP1 receptors and potentiate insulin receptor -subunit signalling, adipokine-based agents such as adiponectin receptor agonists, and AMPK activators. Many compounds have progressed into clinical studies and an analysis of ClinicalTrials.gov in February, 2014, has identified 180 trials registered for drugs to treat diabetes and its complications. However, most of the drugs that are advanced in development are different formulations of existing drugs or new members of existing classes with modest pharmacokinetic modifications. Entirely new interventions to address the underlying aetiopathogenic lesions of type 2 diabetes remain elusive.

Conclusion
Glycaemic control is crucial to the successful management of type 2 diabetes, but despite the variety of differently acting glucose-lowering drugs available, reversing the disease process and reinstatement of normal glucose homoeostasis is rarely possible. The need for multiple treatments has given rise to many new fixed-dose combinations of existing agents and further fixed-dose combinations are envisaged. Innovative approaches with preclinical proof of concept include fatty acid receptor agonists and other novel interventions to promote -cell function, chimeric designer peptides with pancreatic, satiety and thermogenic effects, small molecules to activate GLP1 receptors and potentiate insulin receptor -subunit signalling, adipokine-based agents such as adiponectin receptor agonists, and AMPK activators. AAT received grants from National Institute for Health Research and the Department of Health.

Contributors
All authors contributed to all aspects of this work.

Declaration of interests
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