New therapies for the treatment of type 2 diabetes: an update

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Summary
In type 2 diabetes, several lesions have been identified and drugs are being developed that target these lesions. This review considers agents that have been introduced to Europe since 2006, particularly the glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 inhibitors (gliptins) that represent new classes of agent, both of which target the enteroinsular axis. The GLP-1 analogues and gliptins reduce hyperglycaemia without promoting weight gain, with the former being associated with weight loss. Agents advanced in development, new fixed-dose combination tablets and new formulations of established agents are also considered.

Key words
Type 2 diabetes; GLP-1 analogues; gliptins; DPP-4 inhibitors; SGLT-2 inhibitors

Introduction

Diabetes has been recognised for millennia, but it was not until the 20th century that patients were able to benefit from treatments that went beyond strict dietary regimens and traditional herbal remedies. The advent of insulin therapy in 1923 was a major advance, but not a cure, and the scientific interest in plants as potential therapeutic options led to an unsuccessful search for a botanical source of insulin. Plants did indeed yield glucose-lowering entities that were often investigated as adjuncts to insulin therapy, but were more particularly considered in the treatment of what is now recognised as non-insulin-requiring type 2 diabetes.[1] The advent of insulin therapy helped to differentiate type 1 and type 2 diabetes, due to its life-saving actions in the former and observations that very high insulin doses were needed in patients with the latter. This review will focus on treatments for type 2 diabetes.

Established oral antidiabetic agents

The late 1950s saw the introduction of the sulphonylureas and biguanides (buformin, metformin and phenformin) as therapies for type 2 diabetes. Sulphonylureas are still widely used, and over the years the onset and duration of action and side-effect profiles of these agents have been refined. Metformin is the only biguanide in general use and is now the most widely prescribed antidiabetic agent worldwide – its acceptability being endorsed by its introduction to the USA in 1994. Today, metformin is the preferred first-line drug treatment for type 2 diabetes worldwide.

In the 1990s alpha-glucosidase inhibitors were introduced for the treatment of type 2 diabetes, and the early 21st century heralded the availability of the current thiazolidinediones (rosiglitazone and pioglitazone) and meglitinides (repaglinide and nateglinide). The main actions of established oral antidiabetic agents are summarised in Table 1.[2,3]

Newer approaches to treatment

Newer additions to the antidiabetic armamentarium are pramlintide, the incretin mimetics (notably the GLP-1 analogues), the gliptins, and most recently bromocriptine, which received regulatory approval in the USA in May 2009.[3,4]

Pramlinitide

The soluble amylin analogue pramlintide (Symlin) was the first new class of antidiabetic agent to receive regulatory approval in the 21st century. It was also the first non-insulin treatment for diabetes to be administered by injection. Pramlintide offers a novel mechanism of action that improves glycaemic control whilst aiding weight loss (Figure 1).

Amylin is a pancreatic hormone that is normally co-secreted with insulin, and its secretion diminishes in tandem with the reducing insulin secretion of diabetes. Amylin (insulin amyloid polypeptide) most notably suppresses glucagon secretion (when not normalised by insulin alone) and thereby dampens hepatic glucose output, which reduces postprandial hyperglycaemia. Amylin also reduces hyperglycaemia via effects on gastric emptying, digestion and satiety.[3–5]

Pramlintide received regulatory approval in the USA in 2005 as an adjunct to mealtime insulin therapy in people with type 1 and type 2

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diabetes (with or without sulphonylurea and/or metformin treatment) who cannot achieve adequate glycaemic control despite optimal use of insulin. It is not available in Europe.

Incretin mimetics

Intestinal, or incretin, hormones are released in response to nutrient absorption. They form the basis of the enteroinsular axis and have a range of effects including stimulation of insulin release. However, they are not associated with hypoglycaemia due to the glucose-dependent nature of their release. Incretin hormone-based therapies also offer the advantages of a short duration of action, only acting on specific receptors in target cells, having extra-pancreatic effects that lower hyperglycaemia and potentially increase beta-cell mass, insulin biosynthesis and beta-cell survival.[3,4,6]

GLP-1 analogues

To date, GLP-1 is the only incretin hormone to have a developed therapeutic modality. In type 2 diabetes meal-stimulated GLP-1 release is reduced, but the glucoregulatory response to food is improved following GLP-1 injection. GLP-1 only has a half-life of less than two minutes, as it is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1 analogues are being developed that have a longer half-life than endogenous GLP-1.

The GLP-1 analogues offer the advantages of improving glycaemic control whilst aiding weight loss, and not causing hypoglycaemia when taken as monotherapy.

Exenatide: Exendin-4, a polypeptide with similar glucoregulatory properties to GLP-1 (Figure 2), was originally isolated from the saliva of the Gila monster (a lizard native to the Arizona desert). This gave rise to the synthetic GLP-1 analogue exenatide (Byetta), which is about 48% homologous to native human GLP-1. Exenatide received regulatory approval in the USA in 2005, and in 2006 became the first new class of antidiabetic agent for the treatment of type 2 diabetes to receive regulatory approval in the EU. It is resistant to breakdown by DPP-4, resulting in a half-life of about 2.4 hours. Since it is a peptide, it should be stored at 2–8°C (36–46°F) and administered by injection. It is available in reusable, prefilled, fixed-dose (5µg or 10µg) injection pens. It is recommended for twice-daily injection – before breakfast and evening meal – up to an hour before the meal. It is usual to uptitrate the exenatide dose to reduce the risk of nausea associated

Class of agent	Main action
Sulphonylurea	↑ insulin secretion
Meglitinide (prandial insulin releaser)	↑ insulin secretion*
Biguanide (only metformin)	↓ insulin resistance
Thiazolidinedione (glitazone)	↑ insulin sensitivity
Alpha-glucosidase inhibitor	↓ rate carbohydrate digestion
*More rapid onset and shorter duration of action than sulphonylureas	

Table 1. Main actions of established oral antidiabetic agents

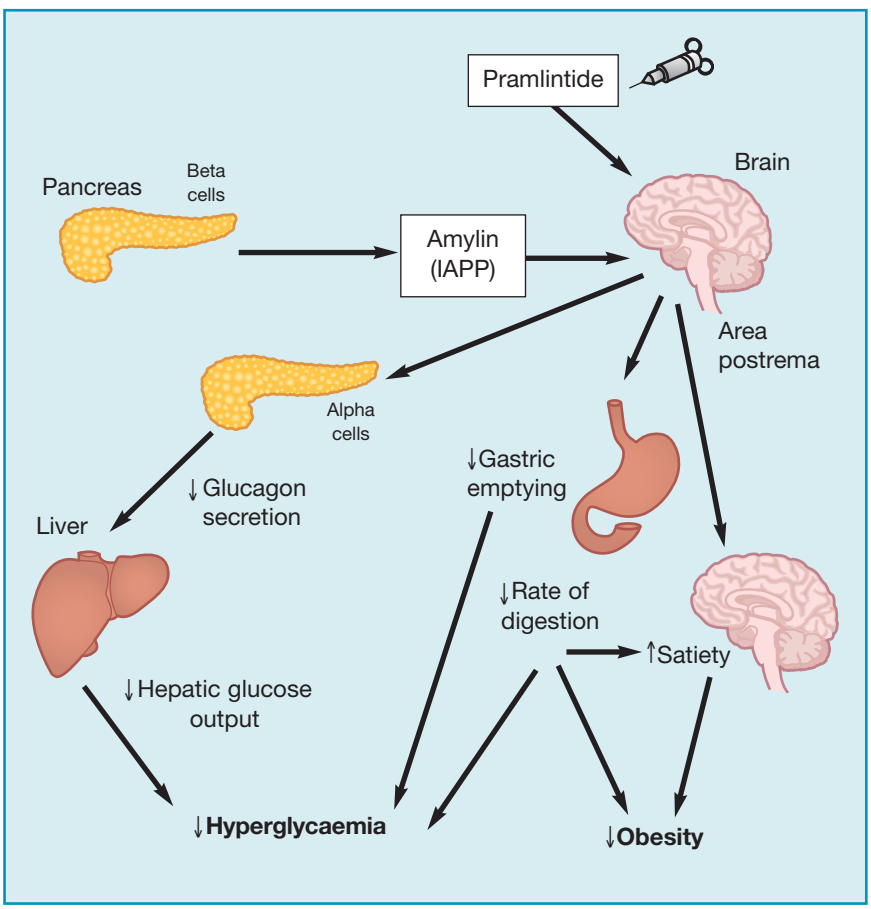

Figure 1. Sites of action of amylin/pramlintide to reduce hyperglycaemia and weight gain (adapted with permission from CJ Bailey)

with this treatment. Exenatide can be used with metformin and/or sulphonylureas. If exenatide is being added to sulphonylurea therapy, the tablet dosage should be decreased to reduce the risk of hypoglycaemia.[3,4,6]

In the presence of glucose, exenatide, like GLP-1, decreases hyperglycaemia by reducing glucagon secretion and increasing insulin secretion, whilst slowing gastric emptying and increasing satiety. These latter effects aid weight loss, thereby permitting improved glycaemic control without the associated weight gain, making this an attractive therapeutic option for patients, despite the need for injection. However, due to local restrictions, exenatide is not prescribed to all patients who might benefit from it, for example the NICE guidelines (for England, Wales and Northern Ireland) only recommend exenatide for people with a body mass index (BMI) >35.

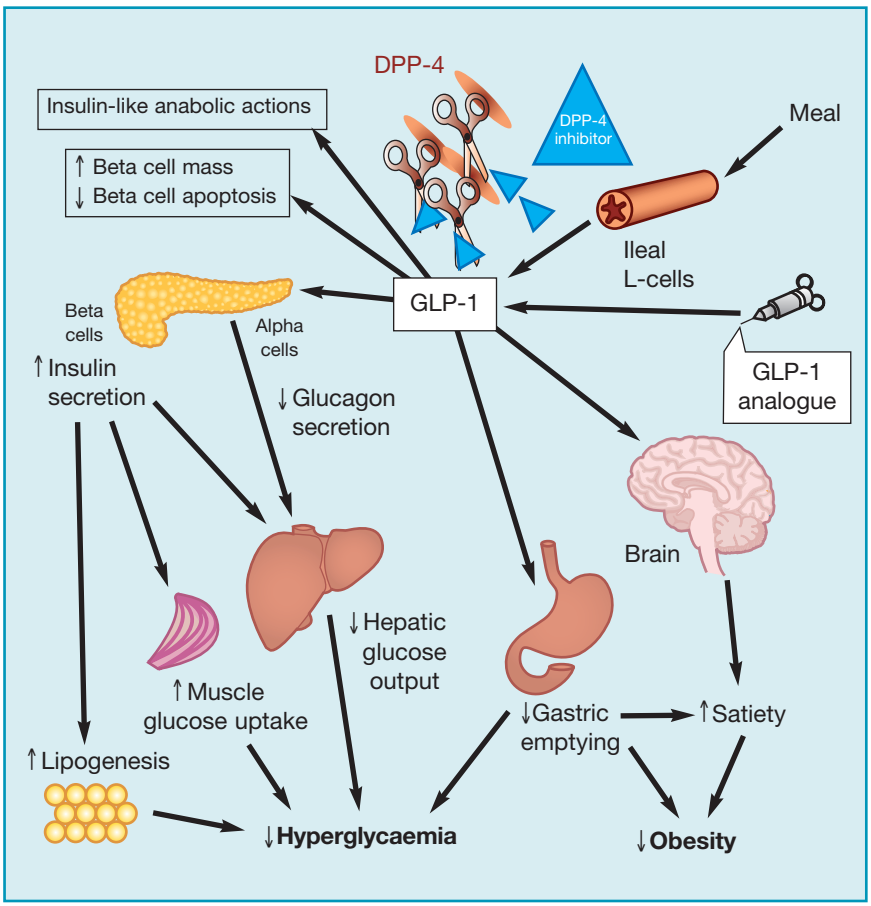

Figure 2. Sites of action of GLP-1, GLP-1 analogues and gliptins to reduce hyperglycaemia and weight gain (adapted with permission from CJ Bailey)

Liraglutide: In April 2009, the Medicines and Healthcare Products Regulatory Agency (Committee for Medicinal Products for Human Use; CHMP) adopted a positive opinion of the use of liraglutide (Victoza) in the treatment of type 2 diabetes, and EU marketing authorisation has now been authorised. Liraglutide is a human GLP-1 analogue that is 97% homologous to native GLP-1. It has a fatty acid (palmitic acid) attached so that, after subcutaneous injection, as it enters the blood stream it binds to albumin. This protects it from breakdown by DPP-4 and extends its half-life to 11–15 hours, such that only a once-daily injection is required. When the drug detaches from the albumin, it acts in the same way as native GLP-1 (Figure 2). Liraglutide will be available in a cartridge-filled pen device similar to the flex pen that will allow three doses to be dialled: 0.6mg, 1.2mg and 1.8mg. It is recommended to begin with the lowest dose and expect to titrate up over several weeks to the 1.2 or 1.8mg dose. Slow titration should minimise the transient nausea experienced by many patients.[4] Indeed, nausea was the most reported side-effect (25.5% and 28%, respectively) in a head-to-head trial of liraglutide (1.8mg once a day) and exenatide (10µg twice a day).[7] However, the percentage of patients reporting nausea declined over the course of the study.

The glucose-lowering efficacy of liraglutide has been assessed in a series of phase III trials known as the Liraglutide Effect and Action in Diabetes (LEAD) trials. These are summarised in Table 2. Most of the clinical studies have been undertaken in obese patients; therefore, the most likely use of liraglutide will be as an add-on therapy for this patient group. However, the CHMP-approved indication for liraglutide is in combination with: metformin or a sulphonylurea, metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients with type 2 diabetes who are unable to achieve adequate glycaemic control with maximal use of these monotherapy or dual therapy combination regimens. The CHMP noted that headache was common in patients taking liraglutide and metformin, and vomiting was common in those taking liraglutide, and metformin and rosiglitazone. Hypoglycaemia was also a common side-effect when liraglutide was

	Mean decrease from baseline			
	HbA_{1c} %	FPG (mmol/l)	Weight (kg)	Proportion achieving HbA_{1c} <7%
LEAD 1 26 weeks	Add-on to glimepiride (versus rosiglitazone and placebo) At baseline mean HbA_{1c} 8.4%, BMI 30			
Liraglutide 1.8mg	1.13	1.59	0.23	40%
LEAD 2 26 weeks	Add-on to metformin (versus glimepiride and placebo) At baseline mean HbA_{1c} 8.4%, weight 88.6kg			
Liraglutide 1.8mg	1.00	1.69	2.79	42%
LEAD 3 52 weeks	Liraglutide as monotherapy (versus glimepiride) At baseline mean HbA_{1c} 8.3%, BMI 33.1			
Liraglutide 1.8mg	1.14	1.42	2.45	51%
LEAD 4 26 weeks	Add-on to metformin + rosiglitazone (versus placebo). At baseline HbA_{1c} 8.3%, BMI 33.5			
Liraglutide 1.8mg	1.48	2.4	2.02	58%
LEAD 5 26 weeks	Add-on to metformin + glimepiride (versus glargine and placebo) At baseline mean HbA_{1c} 8.2%, BMI 30.5			
Liraglutide 1.8mg	1.33	1.55	1.81	52%
LEAD 6 26 weeks	Add-on to metformin and/or a sulphonylurea (versus exenatide) At baseline mean HbA_{1c} 8.2%, BMI 32.9			
Liraglutide 1.8 mg	1.12	1.61	3.24	54%

BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin

Table 2. Action of liraglutide on glycaemic control and body weight in the LEAD studies

added to metformin and glimepiride dual therapy.

Gliptins

The DPP-4 inhibitors are also known as gliptins or incretin enhancers. As noted above, endogenous incretin hormones are rapidly degraded by the enzyme DPP-4, but gliptins inhibit the action of DPP-4, and this extends the availability of endogenous incretin hormones, including GLP-1, in the circulation, and thereby improves glycaemic control (Figure 2). DPP-4 is present in the blood and in several tissues – notably in the gastrointestinal tract, pancreas and kidneys. Thus, in addition to extending the half-life of incretin hormones, gliptins may also upregulate other peptides, which might benefit glycaemic control. An interesting feature of gliptin treatment is that glycaemic improvements are not associated with changes in body weight.[3,4,6]

Sitagliptin (Januvia), vildagliptin (Galvus) and saxagliptin (Onglyza) are available in Europe, where they received regulatory approval in March and September 2007 and October 2009, respectively. They offer the advantages of improving glycaemic control without causing weight gain and are not associated with hypoglycaemia when administered as monotherapy.[3,4] To avoid hypoglycaemia, it may be necessary to reduce the sulphonylurea dose when adding in a gliptin.

Sitagliptin

In July 2006, Mexico became the first country in the world to have access to this new class of agent, and in April 2007 the UK spearheaded the entry of sitagliptin to Europe.

In Europe sitagliptin is now indicated for use as an add-on therapy, where appropriate, to metformin, sulphonylurea or thiazolidinedione therapy, and as triple therapy with metformin and a sulphonylurea. Sitagliptin is available as a 100mg tablet and is a once-daily therapy that can be taken with or without food. When sitagliptin was added to metformin or pioglitazone in 24-week registration trials in patients with type 2 diabetes, mean glycosylated haemoglobin (HbA_{1c}) was reduced by about 0.7% and body weight did not change. Additionally, two-hour postprandial glucose was decreased by about 3mmol/l. The incidence of hypoglycaemia was similar to that reported on addition of placebo.[3,4,8]

Nearly 80% of sitagliptin is excreted unchanged in the urine, and it is important to avoid use in patients with moderate or severe renal insufficiency (creatinine clearance <50ml/min). Since hepatic metabolism of sitagliptin is minor, it has a low propensity for drug interactions, but monitoring is advisable with concomitant administration of digoxin.

Sitagliptin plus metformin: A fixed-dose combination tablet of sitagliptin plus metformin (Janumet) received regulatory approval in Europe in July 2008 for patients inadequately controlled on metformin monotherapy, or in those already receiving metformin and sitagliptin as dual therapy and in combination with a sulphonylurea (*ie* triple therapy). The film-coated tablets contain 50mg sitagliptin with 850mg or

1000mg metformin, and precautions associated with the use of the individual agents apply to the combination tablet. The tablets should be taken with food to avoid gastrointestinal discomfort associated with metformin.[9]

Vildagliptin

This became available in March 2008 and is now for use in combination with metformin or a sulphonylurea or a thiazolidinedione in patients who are inadequately controlled on these agents alone. Vildagliptin is available as 50mg tablets and the daily dose should not exceed 100mg. It can be taken with or without a meal. When used in combination with a sulphonylurea, it is recommended that 50mg vildagliptin is administered in the morning – interestingly, in this patient population vildagliptin 100mg daily is no more effective than vildagliptin 50mg daily. However, when added to metformin or a thiazolidinedione, administration of one dose of 50mg vildagliptin in the morning and in the evening is recommended. When vildagliptin (50mg twice daily) was added to metformin or pioglitazone in 24-week registration trials, HbA_{1c} was reduced by 1.1% and 0.7%, respectively,[10] body weight did not change and hypoglycaemia was rare.[3,4,11] Vildagliptin is excreted mainly in the urine, so patients require adequate renal function (creatinine clearance ≥50ml/minute). Vildagliptin should not be used in patients with hepatic impairment. Rare cases of hepatic dysfunction have been reported; therefore, it is recommended that liver function tests should be performed prior to initiating therapy and at three-monthly intervals for the first year of treatment. Treatment is inappropriate in patients with elevated aspartate transaminase or alanine transaminase more than or equal to three times the upper limit of normal. Nevertheless, there are no recognised drug interactions with vildagliptin.

Vildagliptin plus metformin: A fixed-dose combination tablet of vildagliptin plus metformin (Eucreas) received regulatory approval in Europe in November 2007. It is indicated for patients who are already taking vildagliptin and metformin as separate tablets, and for patients on metformin monotherapy who require dual therapy. The film-coated fixed-dose combination tablet contains 50mg vildagliptin with 850mg or 1000mg metformin. The precautions associated with vildagliptin and metformin should be observed and it is advisable to take the tablet with food to avoid metformin-associated gastrointestinal discomfort.[9]

Saxagliptin

This has now received marketing authorisation in Europe. Saxagliptin (Onglyza) was approved as dual therapy with metformin, a sulphonylurea or a thiazolidinedione in October 2009. In 24-week trials in patients with type 2 diabetes, saxagliptin (2.5mg, 5mg, 10mg) decreased HbA_{1c} by around 0.6%.[12] As with the other gliptins, saxagliptin is excreted mainly via the kidneys, is weight neutral, and is not associated with hypoglycaemia when used as monotherapy.[13]

Bromocriptine

The dopamine agonist bromocriptine (Cycloset) is the latest agent to be added to the oral antidiabetic armamentarium in the USA, where it received approval for the treatment of type 2 diabetes in May 2009. It should be taken in the morning, within two hours of waking, and be uptitrated by one tablet (0.8mg) a week as necessary to a maximum of 4.8mg, to avoid gastrointestinal disturbance, notably nausea. This treatment has several contraindications and associated warnings and precautions. In 24-week registration studies, bromocriptine reduced HbA_{1c} by up to 0.5% and was not associated with hypoglycaemia.[14]

New formulations

The availability of generic agents and its positioning as a first-line treatment have led to the promiscuity of metformin: it is the partner in all but one (rosiglitazone plus glimepiride) of the fixed-dose combination tablets for the treatment of type 2 diabetes.[9] The gastrointestinal disturbances associated with metformin can be reduced or eliminated by using a slow-release formulation (available as Glucophage SR 500mg, 750mg and 1000mg). Liquid formulations of metformin (500mg/ml) are also available for those who have difficulty swallowing tablets. In the UK, sachets of powdered metformin (Glucophage powder 500mg and 1000mg) became available in April 2009. The powder rapidly dissolves in water and contains excipients to mask the otherwise bitter/metallic taste.

New classes of agents

Several classes of agents are being investigated as potential antidiabetic drugs. Agents affecting renal elimination of glucose are the most advanced in development.

SGLT-2 inhibitors

Glycosuria is indicative of hyperglycaemia. A natural mechanism to reduce hyperglycaemia is to eliminate glucose via the urine. Under normal conditions, filtered glucose is reabsorbed from the proximal renal tubule, mainly via the action of sodium-glucose cotransporter 2 (SGLT-2). If SGLT-2 is inhibited,

the filtered glucose passes into the urine. SGLT-2 is found only in the proximal renal tubule, and specific inhibitors are being developed that allow excess glucose to pass through the tubule for elimination in the urine.[15] Dapagliflozin is the SGLT-2 inhibitor most advanced in development.

In a 12-week study in patients with type 2 diabetes taking oral insulin sensitisers and 50% of their daily insulin dose, the addition of dapagliflozin (10mg or 20mg) reduced HbA_{1c} by around 0.7%.[16] Improvements in glycaemic control were observed whilst achieving concomitant weight loss of about 2kg, facilitated by urinary loss of glucose accounting for 200–300kcal/day.[17] To date, adverse effects have been similar to those observed in placebo-treated patients, although there has been a slight increase in the incidence of urinogenital infections.

Lost agents

The inhaled insulin Exubera appeared briefly, but was withdrawn in October 2007. This was originally presumed to be due to financial constraints imposed by a poor take-up of this product. However, in 2008 it became evident that there was an increased incidence of primary lung malignancies in patients who had taken Exubera during the registration trials.[18]

2007 also saw the discontinuation of Novo Nordisk's animal insulin preparations, followed by the discontinuation of Mixtard 10, 20, 40 and 50, and most recently velosulin. These losses have essentially been prompted by the successful use of human and analogue insulin preparations.

After less than two years, the anti-obesity agent rimonabant (Acomplia) was withdrawn due to concerns surrounding anxiety, depressive disorders and suicidal ideation. This first-in-class cannabinoid receptor antagonist reduced HbA_{1c} (often >0.5%) and improved the cardiovascular risk profile in obese patients with type 2 diabetes to a greater extent than would be expected by weight loss (about 4kg) alone.[19] The development of other agents in this class, *eg* taranabant, has also been discontinued.

Conclusions

The journey from bench to bedside takes decades, and even with regulatory approval the viability of an agent is not secure. Saxagliptin and liraglutide are the antidiabetic agents most advanced in the regulatory process, but they both belong to classes of agent that are becoming established. The SGLT-2 inhibitors, represented by dapagliflozin, are currently the most likely agents to offer a new mechanistic approach to the treatment of type 2 diabetes in the not too distant future.

Conflict of interest statement:
None

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