



Pharmacological therapies for type 2 diabetes: future approaches

Clifford J. Bailey¹

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Abstract

Despite the availability of at least nine differently acting classes of glucose-lowering agents, many people with type 2 diabetes do not achieve or maintain sufficiently tight glycaemic control to avoid the complications of chronic hyperglycaemia. This narrative review examines the prospects for future non-insulin agents and therapeutic approaches in early development that aim to improve glycaemic control in type 2 diabetes. Such therapies will ideally enhance glucose lowering through existing mechanisms or by targeting different aspects of disease pathophysiology. They will avoid overt hypoglycaemia and facilitate weight control and be convenient to use, have minimal adverse effects, provide benefits against common comorbidities and have a commendable overall safety profile. Particularly promising therapies in development are the co-agonist and multi-agonist incretin-based and amylin-based synthetic peptides that improve glycaemic control and body weight regulation. Initial studies suggest that such therapies can improve insulin secretion, assist pancreatic beta cell preservation and enhance insulin-mediated glucose metabolism while reducing glucagon secretion and risk of fatty liver disease. Antibodies and small molecules that interact with incretin targets are also being developed, as well as agents to modulate mitochondrial function, fatty acid receptors and receptors for selected gastrointestinal and adipocyte peptides that affect appetite or pathways of nutrient metabolism. Multiomics, miRNAs, gene-editing technologies and epigenetic targets have received considerable attention but have yet to deliver usable therapies. Directing therapeutic agents to specific organs or tissues and avoiding unwanted off-target effects continue to challenge the application of laboratory innovations into viable clinical agents. However, recent successes with weight-lowering incretin-based medicines have raised expectations for pharmaceutical pipelines to transform the management of type 2 diabetes.

Keywords Amylin · Glucagon · Glucose lowering · Incretin · Insulin action · Insulin secretion · Review · Therapies · Type 2 diabetes

Abbreviations

CCK	Cholecystokinin
FFAR	Free fatty acid receptor
FGF21	Fibroblast growth factor-21
GCGR	Glucagon receptor
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
MASLD	Metabolic dysfunction-associated steatotic liver disease
SGLT	Sodium–glucose cotransporter
SNAC	Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate

Introduction

There are presently nine classes of glucose-lowering agents used in the treatment of type 2 diabetes in Europe and several more are available in other regions (Table 1) [1, 2]. Lifestyle changes (principally diet, exercise and behavioural interventions) underpin all treatment algorithms. Non-insulin pharmacological agents use different glucose-lowering mechanisms and can be used as monotherapy or in combination, while insulin provides the default medicine for the most advanced stages of this progressive disease [2–4]. Different agents can address different aspects of disease pathophysiology, intervene against complications and comorbidities, and act in parallel to facilitate a personalised therapeutic approach. However, normal glucose homeostasis is seldom reinstated. In surveys, >40% of individuals with type 2 diabetes typically fail to achieve or maintain recommended targets for HbA_{1c} and almost all eventually

✉ Clifford J. Bailey
c.j.bailey@aston.ac.uk

¹ Health and Life Sciences, Aston University, Birmingham, UK

Table 1 Key features of the main glucose-lowering agents used in the management of type 2 diabetes

Class with examples ^b	Mode of action	(a) Glucose-lowering efficacy ^a (b) Hypo risk ^a (c) Weight effects ^a	(a) Cardiorenal effects (b) Cautions and limitations (c) Additional effects or comments
Oral			
Biguanide (metformin [IR, SR/XR formulations])	Counter insulin resistance: reduce hepatic glucose output, increase splanchnic glucose turnover, increase insulin-mediated glucose metabolism	(a) Efficacy high (b) Hypo risk low (c) Weight neutral	(a) Decrease CV mortality rate, increase survival rate, no evident effect on renal function but adequate renal function required for drug clearance (e.g. ≥ 30 ml/min per 1.73 m ²) (b) Check renal function. Interrupt if using contrast media. Avoid in renal or liver impairment, sepsis, hypoxaemia, history of lactic acidosis or alcohol abuse. Rare risk of lactic acidosis. Check vitamin B ₁₂ in long-term use (c) Possible reduced risk of some cancers
Sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide)	Stimulate insulin secretion (typical duration 6–24 h)	(a) Efficacy high (b) Hypo risk moderate (c) Weight gain	(a) Clinically significant cardiorenal effects not established (b) Avoid in renal or liver impairment depending on elimination route of agent. Self-monitor blood glucose if driving or operating machinery (c) Glucose-lowering efficacy declines with advancing beta cell dysfunction
Meglitinides (nateglinide, repaglinide)	Stimulate insulin secretion (rapid- and short-acting duration <6 h)	(a) Efficacy intermediate (b) Hypo risk moderate (c) Weight gain	(a) Clinically significant cardiorenal effects not established (b) Avoid in liver impairment. Self-monitor blood glucose if driving (c) Take with main meals
DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)	Inhibit DPP-4: prolong half-life of incretin hormones (GLP-1 and GIP), enhance prandial insulin secretion	(a) Efficacy intermediate (b) Hypo risk low (c) Weight neutral	(a) Clinically significant cardiorenal benefit not established (b) Discontinue if acute pancreatitis. Adjust dose in renal impairment except linagliptin (c) Overall good safety profile
Thiazolidinedione (pioglitazone)	Improve insulin action via PPAR γ agonism	(a) Efficacy high (b) Hypo risk low (c) Weight gain	(a) Possible reduced risk of ASCVD, notably stroke (b) Slow onset of action. Risk of oedema, heart failure and bone fractures. Check liver enzymes (a) Reduce onset/progression of heart failure and CKD (b) Check for adequate renal function and hydration. Increased risk of genital and urinary infections and euglycaemic ketosis (c) Diuretic effect, reduction in blood pressure
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	Inhibit SGLT2 in kidney, decrease renal glucose reabsorption, increase glucose elimination in urine	(a) Efficacy intermediate to high (b) Hypo risk low (c) Weight reduction	(a) Clinically significant cardiorenal benefit not established (b) Avoid if gastrointestinal disorders (c) Side effect of flatulence
Alpha-glucosidase inhibitors (acarbose)	Slow rate of carbohydrate digestion, reduce prandial glycaemic excursions	(a) Efficacy intermediate to low (b) Hypo risk low (c) Weight neutral	

Table 1 (continued)

Class with examples ^b	Mode of action	(a) Glucose-lowering efficacy ^a (b) Hypo risk ^a (c) Weight effects ^a	(a) Cardiorenal effects (b) Cautions and limitations (c) Additional effects or comments
Dopamine agonist (bromocriptine)	Dopamine D2 receptor agonist, reduces hepatic glucose output	(a) Efficacy intermediate (b) Hypo risk low (c) Weight neutral	(a) Clinically significant cardiorenal effects not established (b) Avoid if uncontrolled hypertension. Doses and timings used for type 2 diabetes are much lower than in treatment of Parkinson's disease (c) Can improve circadian rhythm of glycaemic control
Bile acid sequestrant (colesevelam)	Binds bile acids in intestine, interrupts enterohepatic bile acid circulation; alters microbiome, increases secretion of GLP-1	(a) Efficacy low (b) Hypo risk low (c) Weight neutral	(a) Possible reduced risk of ASCVD (b) Avoid if obstructive gastrointestinal disease, pancreatitis, ketosis, hypertriglyceridaemia (c) Reduces hypercholesterolaemia. May interfere with absorption of vitamins and minerals
Subcutaneous injection			
GLP-1 receptor agonists (dulaglutide, exenatide QW, liraglutide, semaglutide, semaglutide oral, tirzepatide)	Activate GLP-1 receptors, potentiate glucose-induced insulin secretion, decrease glucagon secretion, increase satiety, delay gastric emptying	(a) Efficacy high or very high (b) Hypo risk low (c) Weight reduction	(a) Typically reduce albuminuria and some agents in class significantly reduce ASCVD and CV deaths (b) Initial nausea, titrate as appropriate. Discontinue if acute pancreatitis (c) Reduce blood pressure
Amylin analogue (pramlintide)	Increase satiety, delay gastric emptying, decrease glucagon secretion	(a) Efficacy intermediate (b) Hypo risk low (c) Weight reduction	(a) Clinically significant cardiorenal benefit not established (b) Initial nausea; avoid if gastroparesis, caution if hypoglycaemia unawareness (c) Only used as prandial adjunct to insulin therapy
Insulin (ultra-rapid acting: Fiasp, Lyumjev; rapid acting: Aspart, Glulisine, Lispro; short acting: Actrapid, Humulin S, Insuman Rapid; intermediate: Insulatard, Humulin I; long acting: degludec, glargine; very long acting: icodec; biphasic (premixed): Humalog, Humulin M3, Novomix)	Promote peripheral glucose uptake, glycogenesis and metabolism, decrease gluconeogenesis, increase lipogenesis, decrease lipolysis, increase protein synthesis, decrease protein catabolism, involvement in cell growth, division and differentiation	(a) Efficacy very high (b) Hypo risk high (c) Weight gain	(a) Clinically significant cardiorenal benefit not clear, although acute effects to improve vasorelaxation and reduce atherogenesis and thrombus formation (b) Important to align treatment regimen with patient lifestyle and needs. Requires appropriate lifestyle adjustments and glucose monitoring, especially if driving or operating machinery (c) High risk of hypoglycaemia: carry glucose. Increase renal sodium reabsorption

^aBased on ADA/EASD and American Association of Clinical Endocrinology (AACE) consensus statements [2–4]

^bSemaglutide is listed as an injection but is also available as an oral formulation. Some agents are not available in all countries; dosage forms and prescribing information listed in the summary of product characteristics may vary between countries. Additional agents (not listed here) have indications as glucose-lowering agents outside Europe and North America. Exenatide BD and lixisenatide have recently been discontinued. Tirzepatide is a GLP-1/GIP dual receptor agonist but is listed under GLP-1 receptor agonists for the purposes of this review. Fixed-dose combinations of oral agents (e.g. single tablet combinations of metformin with a DPP-4 inhibitor, sulfonylurea, pioglitazone or SGLT2 inhibitor) and fixed-ratio injectable combinations of a GLP-1RA with insulin are available. Premixed insulins and biosimilar insulins (not listed in this table) are also available. Note that in Europe the composition of a premixed insulin is described with the short-acting component before the long-acting component, whereas the description is the other way around in some countries (e.g. USA). Detemir (not listed in the table) and insulatard cartridges are being discontinued through 2025–2026. ASCVD, atherosclerotic CVD; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; hypo, hypoglycaemia; IR, immediate release; MR, modified release; PPAR γ , peroxisome proliferator-activated receptor-gamma; QW, once weekly; SGLT, sodium–glucose cotransporter; SR, sustained release; XR, extended release

develop a micro- and/or macrovascular complication associated with inadequate metabolic control (electronic supplementary material (ESM) Appendix 1). These shortcomings highlight the need for further, differently acting and more effective therapies that are complementary to and compatible with existing agents and that have acceptable long-term safety profiles (ESM Appendix 2).

This narrative review considers potential new non-insulin pharmacological approaches to glycaemic control including agents in clinical development and examples of preclinical research that illustrate novel mechanisms. Lessons learned from several initiatives that have not proceeded in development are described in ESM Appendix 3.

Unmet needs

In principle, an understanding of disease pathophysiology and the limitations of existing therapies (ESM Appendix 2) will identify unmet needs and point to potential novel pharmacological targets. However, the history of diabetes medications illustrates how clinical serendipity has been as productive as molecular modelling, logical scientific design and mass screening for active compounds [5]. Current clinical guidance reminds us that phenotypic presentations of type 2 diabetes are highly variable but that there are common unmet needs and conformities in therapeutic strategy [2–4]. Hyperglycaemia (as a marker of defective glucose homeostasis) is a fundamental feature linked to retinopathic, neuropathic and nephropathic complications, and a contributing risk for associated morbidities, particularly cardiovascular diseases. Thus, improved glycaemic control is recognised as a crucial therapeutic objective. Accordingly, the areas of unmet need for new treatments are reflected in the lesions that underly the hyperglycaemia, notably impaired function and number of pancreatic beta cells, insulin resistance and glucose toxicity, which are frequently aggravated by excess adiposity, abnormalities of glucagon secretion, an altered incretin response and disturbances in lipid metabolism [6].

Regarding pancreatic beta cell defects, there are particular needs to restore first-phase glucose-induced insulin release and improve proinsulin-to-insulin processing, as neither problem is adequately addressed by existing therapies. General interventions are required to protect against cytotoxic damage to beta cells (e.g. by proinflammatory factors and products of metabolic stress) and specifically to counter the declining beta cell population using therapies that reduce beta cell apoptosis or replenish through beta cell neogenesis.

Insulin resistance impairs nutrient metabolism and vascular function but usually responds well to reduced adiposity. However, additional therapies are required to circumvent rate-limiting steps within the signalling pathways of insulin action or to intervene directly in cellular glucose metabolism

to reduce excess glucose production, improve peripheral glucose disposal and reduce glucotoxicity. Excess adiposity is a particular overarching challenge in the treatment of type 2 diabetes because weight control can benefit so many of the other unmet needs by reducing metabolic stress to beta cells, improving insulin sensitivity and independently reducing the risk of associated morbidities [6]. Recently available satiety-inducing incretin-based medicines are already revolutionising obesity management and greatly improving glycaemic control in type 2 diabetes [7].

An ideal new agent will provide durable blood glucose-lowering efficacy that is better than or similar to that of available agents, carry minimal risk of overt hypoglycaemia, facilitate weight control and hopefully provide some further advantages, particularly against associated morbidities. Such an agent will probably have a different and complementary mode of action that enables use in combination therapy, and/or be conducive to use in clinical circumstances that are less well served by existing agents, for example in obesity, atherosclerotic CVD, heart failure, chronic kidney disease, frail sarcopenia and other conditions commonly encountered among those with type 2 diabetes [1]. Tolerability, ease of administration, minimal monitoring requirements and cost are also important determinants of acceptability, and preventive advantage for individuals with impaired glucose tolerance would be very desirable. Above all, the long-term safety profile must provide a strongly favourable balance of benefit over risk. A summary of potential agents considered in the following sections is provided in Fig. 1.

While new therapies can address aspects of need relating to disease pathophysiology, they do not necessarily obviate barriers that are known to preclude optimal use of existing therapies [8]. For example, from the patient perspective, inadequate health literacy, financial constraints, phobias, fear of hypoglycaemia, and social, cultural or personal pressures can adversely impact lifestyle and treatment adherence. From a clinician perspective, inappropriately structured healthcare provision, scarcity of resources, educational requirements, delayed diagnosis and treatment inertia also represent significant challenges. Advances in drug delivery (e.g. slow-release tablet formulations, once-weekly injections, pumps and transdermal patches), fixed-dose combinations, the reassurance of continuous glucose monitoring, digital aids and educational programmes can reduce some of these barriers, but new therapies alone cannot guarantee universal appeal, acceptance or proper use.

Pragmatic considerations

Although the underlying principles of drug development are conveniently categorised into a series of preclinical and clinical phases with recognised achievement criteria,

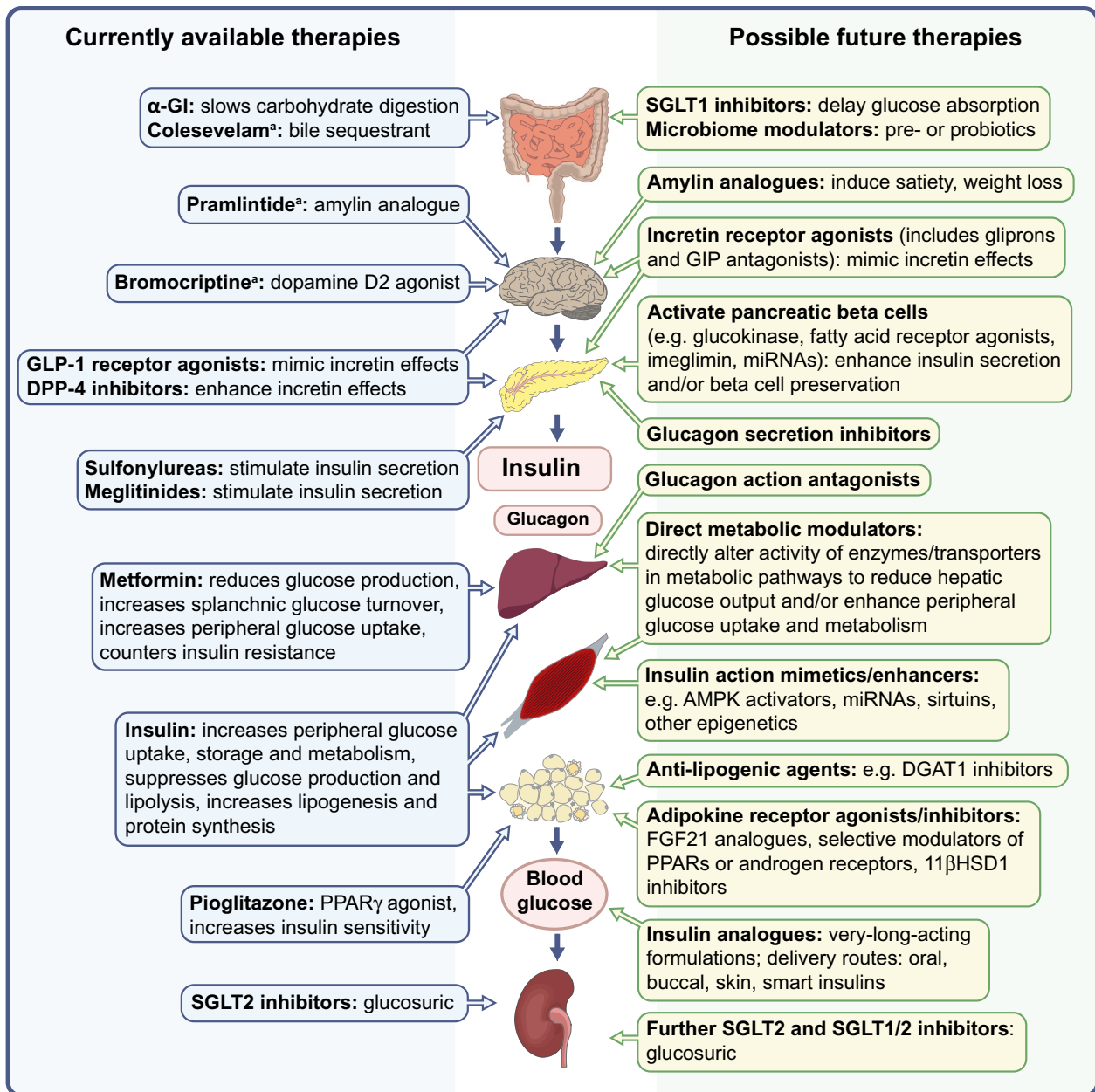


Fig. 1 Sites of action of currently available and potential future glucose-lowering agents for use in the management of type 2 diabetes. ^aNot indicated for glucose-lowering in Europe. 11 β HSD1, 11 β -hydroxysteroid dehydrogenase 1; α -GI, alpha-glucosidase inhibitor; AMPK, adenosine monophosphate-activated protein kinase; DGAT1, diacylglycerol acyltransferase 1; DPP-4, dipeptidyl pepti-

dase-4; FGF21, fibroblast growth factor 21; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptor; QW, once weekly; SGLT, sodium–glucose cotransporter. Adapted from Bailey et al [99] with permission from Elsevier. This figure is available as a [downloadable slide](#)

a new medicine for type 2 diabetes must accommodate several particularly complex challenges [9]. The progressive heterogeneous nature of type 2 diabetes and its broad pathogenic impact may commit a new medicine to lifelong use through varying clinical circumstances that impose diverse safety constraints. Thus, regulatory approval is subject to predefined cardiovascular safety analyses and

usually a post-approval dedicated cardiovascular outcomes trial as well as studies in potentially vulnerable subgroups such as those with chronic kidney disease [3, 4, 9]. For examples of requirements for regulatory approval, see [10, 11]. Development of a new agent from discovery to market usually takes about 10–12 years, but this timespan can vary significantly. Estimating the cost of research and

development for a new agent is complicated by the compounds included and discarded in the process. Phase 3 trials account for the majority of pre-approval expenditure, and estimates of US\$ 1–2.7 billion have been suggested to account for overall expenditure up to completion of submission for regulatory approval [12].

Insulin secretion and beta cell preservation

Many *in vitro* and preclinical studies have examined agents that enhance insulin secretion, including agents that generate ATP, inhibit K⁺-ATP channels, raise cytosolic calcium, activate muscarinic or imidazoline receptors, suppress α 2-adrenergic receptors, inhibit phosphodiesterases to increase cAMP, stimulate phospholipases or modulate various intracellular regulators of insulin exocytosis. However, it has not been possible to specifically target these agents in pancreatic beta cells and exclude extraneous effects [1, 9]. Another problem is that preclinical research has mostly studied interventions at early stages of diabetic syndromes that do not readily apply to more advanced stages of clinical disease. In addition, differences between autoimmune beta cell loss in type 1 diabetes and metabolically driven beta cell loss in type 2 diabetes have warranted different therapeutic approaches to beta cell preservation, although some future initiatives for beta cell neogenesis may be suitable for the treatment of both types of diabetes [13].

Imeglimin

Imeglimin is a tetrahydrotriazine that was recently approved to treat type 2 diabetes in Japan (2021) and India (2022) and which has been shown to improve glucose-induced insulin secretion, especially first phase, in clinical trials [14]. It increases the production of nicotinamide adenine dinucleotide (NAD) via nicotinamide phosphoribosyltransferase (NAMPT) and increases the activity of the mitochondrial respiratory chain to promote ATP synthesis and reduce oxidative stress [15]. Preliminary studies in other tissues suggest that high concentrations of imeglimin may increase the expression of genes encoding respiratory chain complexes 1 and 3 [16]. Imeglimin reduces beta cell apoptosis and maintains beta cell mass when introduced early in the development of diabetes in animal models, possibly by reducing apoptotic cues via effects on mitochondrial viability, but it is not known whether such protection operates in advanced clinical disease [17]. Imeglimin has also been reported to reduce lipotoxicity and inflammation and improve insulin sensitivity [18].

Glucokinase activators

Because the control of glucokinase differs between pancreatic beta cells and liver, allosteric activators (selected to increase glucose affinity) can enhance insulin secretion (including first phase) without an excessive increase in glucose uptake and use by the liver [19, 20]. With careful dose titration and timing to align with meals, the risk of insulin oversupply and hypoglycaemia can be minimised, and several glucokinase activators with variable effects on beta cells vs liver have improved glycaemic control in clinical studies [21]. Dorzagliatin activates glucokinase in pancreas and liver and is approved in China (2022). It enhances the secretion of insulin and glucagon-like peptide-1 (GLP-1) and reduces glucagon secretion. In a 24 week Phase 3 randomised double-blind placebo-controlled trial in drug-naïve individuals with type 2 diabetes, dorzagliatin lowered HbA_{1c} by ~0.6 mmol/mol (0.57%; placebo subtracted) and did not increase hypoglycaemia [22]. In preclinical studies dorzagliatin improved beta cell mass, but most long-term (>6 months) clinical studies with glucokinase activators have noted a loss of effectiveness, providing a reminder that persistently increased glucose stimulation of the beta cell may hasten functional exhaustion and demise [20, 23].

Fatty acid receptor agonists

Pancreatic beta cells and intestinal L cells express several types of G protein-coupled receptors for fatty acids that potentiate the secretion of insulin and GLP-1 [24]. Selective small molecule agonists have been developed to activate many of these receptors, notably G protein-coupled receptor 40 (GPR40 [free fatty acid receptor (FFAR) 1]), GPR119 and GPR120 (FFAR4), and several have shown efficacy in animal models. However, efficacy in clinical studies has been disappointing, possibly because excessive chronic stimulation is associated with receptor internalisation, and some agents have disturbed liver function [25, 26].

miRNAs

The expression of many miRNAs in pancreatic beta cells is altered in diabetic states, providing a potential (if still highly challenging) therapeutic approach [27]. An example of overexpression of an miRNA in type 2 diabetes is miR-200c, which decreases the expression of ETS variant transcription factor 5 (ETV5), causing disruption to insulin exocytosis. Inhibition of miR-200c using an antagomir with complementary nucleotides increased glucose-induced insulin secretion (almost threefold) in islets from type 2 diabetes donors [28]. Several miRNAs

are known to enhance insulin production, reduce beta cell loss and/or promote beta cell proliferation, such as miR-30d (via increased insulin gene expression) and miR-375 (mechanism unclear) [27]. However, delivering miRNAs or inhibitors specifically to beta cells remains a major hurdle for the clinical application of this therapeutic approach [29]. Similarly, the therapeutic potential of miRNA targets to improve insulin action has been compromised by difficulty in restricting agents to selected tissues (ESM Appendix 3).

Other activators of pancreatic beta cells

Incretin hormone receptor agonists (discussed below) can reduce beta cell apoptosis *in vitro* and in animal models, probably via cAMP and protein kinase A (PKA) activation, and provide the best evidence-supported opportunity to preserve the beta cell population at this time. Indeed, GLP-1 receptor agonists (GLP-1RAs) sustain insulin secretion during long-term clinical use, consistent with a direct benefit to the beta cell population [7]. An extensive list of agents including thiazolidinediones, insulin-like growth factors, fibroblast growth factors, gastrin, glycogen synthase kinase-3 β (GSK-3 β) inhibitors, protein kinase dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) inhibitors, gamma-aminobutyric acid, quinolones, sphingosine phosphate, oestrogens and phytoestrogens, polyphenols, flavonoids and other plant compounds has been reported to increase beta cell proliferation *in vitro* or in animal models, but specifically targeting these agents to pancreatic beta cells *in vivo* remains an unfulfilled therapeutic challenge [30].

Cell-based therapies

Although cell-based therapies exceed the remit of this review, some cell-based technologies that might be delivered non-surgically and applied to type 2 (and type 1) diabetes are briefly mentioned here [13]. Preventing beta cell de-differentiation, stimulating proliferation and differentiation of pluripotent stem cells, and enhancing CRISPR-targeted gene editing can be mediated with small molecules and used in conjunction with conventional glucose-lowering therapies. It has long been known that pancreatic centroacinar cells can give rise to new insulin-secreting cells, and preclinical studies have noted that bone morphogenetic protein-7 (BMP7) can induce beta cell neogenesis from pancreatic ductal tissue. Agents that mimic BMP7 or promote BMP7 signalling via the BMP receptor activin-like kinase 3 (ALK3) are being assessed as another (potentially less expensive) approach to islet regeneration [31]. For further information, see [32–34].

Glucagon antagonists

Interventions that suppress prandial glucagon secretion can reduce hyperglycaemia in type 2 diabetes, but timed targeting specifically to pancreatic alpha cells *in vivo* has proved difficult. Antagonising glucagon receptors (GCGRs) with modified glucagon analogues, small molecules or antisense oligonucleotides has also been problematic because of the risk of hypoglycaemia and adverse effects on liver function, including steatosis and an increase in LDL-cholesterol. There is also a compensatory increase in glucagon secretion, which can cause an acute rebound hyperglycaemia if treatment is missed or stopped [35, 36].

GLP-1 receptor agonists

GLP-1 became the focus of incretin therapy because of its strong potentiation of glucose-induced insulin secretion and glucose-lowering efficacy in type 2 diabetes. Accordingly, several analogues (once daily and once weekly subcutaneously injected and once daily oral) with potent GLP-1RA effects are well established within treatment algorithms [2–4, 7]. Use of a GLP-1RA can assist remission from early-stage disease and provide sustained benefits throughout the natural history of the disease, including compatible use with other classes of glucose-lowering agents. Weight loss in particular, but also cardiorenal benefits and other potential advantages, have encouraged wider use, and several further GLP-1RAs with ever longer circulating half-lives are advancing in development, aiming to leverage the convenience of administration with minimal gastrointestinal side effects (Table 2) [37].

Efpeglenatide (a modified exendin conjugated to human immunoglobulin-4 via a polyethylene glycol linker) has shown metabolic efficacy and cardiorenal benefits as a once-weekly subcutaneous injection during Phase 3 trials, but has yet to be progressed further [38]. However, efpeglenatide was also effective as a biweekly and once-monthly subcutaneous injection, illustrating the opportunity to produce ever longer-acting GLP-1RAs for less frequent administration [39]. Another very-long-acting GLP-1RA is ZT002, a GLP-1 analogue with a C-terminal extension to increase stability and two C-18 fatty acid chains to increase attachment to albumin. It has a circulating half-life of ~12 days, which enables biweekly or once-monthly subcutaneous injection [40]. For increased potency, ecnoglutide is a GLP-1 analogue with an Ala8 to Val substitution and a C-18 fatty acid at Lys30. This enables biased agonism at the GLP-1 receptor through increased signalling via cAMP and reduced recruitment of β -arrestin, thereby reducing receptor internalisation [41].

Table 2 Incretin-based and amylin-based peptide and non-peptide (small) molecules in development for the management of hyperglycaemia in individuals with overweight/obesity and type 2 diabetes

Agent (sponsor)	Receptor targets	Route	Timing	Phase ^a	Participants, trial duration, primary trial results ^{b,c}	Reference
Peptide						
Amycretin (Novo)	AmylinRA/GLP-1RA	Oral	OD	1	OW/O, 12 weeks ↓BW 13.1%	[69]
Cagrilintide + semaglutide (CagriSema) (Novo)	AmylinRA + GLP-1RA mix	SC	QW	2	OW/O T2D, 32 weeks ↓HbA _{1c} 2.2% ^d , ↓BW 15.6% ^b	[67]
		SC	QW	3	OW/O, 68 weeks ↓BW 20.4%	[68]
		SC	QW	3	OW/O T2D, 68 weeks ↓HbA _{1c} 1.4%, ↓BW 10.4%	[68]
CT-388 (Roche)	GLP-1RA/GIPRA	SC	QW	1	OW/O, 24 weeks ↓BW 18.8%	[91]
Ecnoglutide (Sciwind)	GLP-1RA	SC	QW	2	NW/OW T2D, 20 weeks ↓HbA _{1c} 2.39%, ↓BW 2.26 kg	[41]
Maridebart cafraglutide (MariTide, AMG133) (Amgen)	GLP-1RA/GIPRI	SC	QM	2	OW/O T2D, 52 weeks ↓HbA _{1c} ~1.5%, ↓BW 10.6%	[55]
		SC	QM	2	OW/O, 52 weeks ↓BW 13.7%	[55]
Mazdutide (Lilly)	GLP-1RA/GCGRA	SC	QW	3	OW/O, 48 weeks ↓BW 13.3%	[59]
Pemvidutide (Altimune)	GLP-1RA/GCGRA	SC	QW	2	OW/O MASLD ± T2D, 12 weeks ↓BW 3.5%, rrLFC 57.1%	[58]
Retatrutide (Lilly)	GLP-1RA/GIPRA/GCGRA	SC	QW	2	OW/O T2D 24 weeks ↓HbA _{1c} 2.01% 36 weeks ↓BW 13.9%	[61]
		SC	QW	2	OW/O, 48 weeks ↓BW 22.1%	[92]
		SC	QW	2	OW/O MASLD, 24 weeks ↓BW 17.6%, rrLFC 82.4%	[93]
Survodutide (BI)	GLP-1RA/GCGRA	SC	QW	2	OW/O, 46 weeks ↓BW 14.9%	[57]
VK2735 (Viking)	GLP-1RA/GIPRA	SC	QW	2	OW/O, 13 weeks ↓BW 13.1%	[94]
		Oral	OD	2	OW/O, 13 weeks ↓BW 10.9%	[95]
ZT002 (Beijing QL)	GLP-1RA	SC	QM	1	OW/O, 14 weeks ↓BW 13.1%	[40]
Non-peptide						
Orforglipron (Lilly)	GLP-1RA	Oral	OD	2	NW/OW/O T2D, 26 weeks ↓HbA _{1c} 1.67%, ↓BW 7.9 kg	[96]
		Oral	OD	3	OW/O T2D, 40 weeks ↓HbA _{1c} 1.07%, ↓BW 5.9 kg	[83]
Aleniglipton (Structure)	GLP-1RA	Oral	OD	2	OW/O, 12 weeks ↓BW 6.2%	[97]
CT-996 (Roche)	GLP-1RA	Oral	OD	1	OW/O, 4 weeks ↓BW 6.1%	[85]
CX11/VCT220 (Corxel)	GLP-1RA	Oral	OD	2	OW/O, 16 weeks ↓BW 8.1%	[86]
Tern-601 (Tern)	GLP-1RA	Oral	OD	1	OW/O, 4 weeks ↓BW 5.0%	[98]

^aFor Phase 3 RCTs, efficacy was calculated as placebo-subtracted change in HbA_{1c} or body weight for the top dose tested

^bIn trials involving individuals with type 2 diabetes, the test agent or placebo was administered as an add-on to lifestyle (diet + exercise) or lifestyle plus metformin. In trials involving individuals without diabetes, the test agent or placebo was administered as an add-on to lifestyle

^cHbA_{1c} decreases are reported in per cent as in most of the original reports. To convert HbA_{1c} values from % to mmol/mol in this table, multiply by 10.929. Thus, 1% is equivalent to 10.929 mmol/mol. This is different to the conversion for absolute values in blood that exceed ~3%, which require multiplication by 10.929 and subtraction of 23.5

^dNot placebo subtracted as there was not a placebo arm in this trial, which compared cagrilintide + semaglutide against cagrilintide or semaglutide alone
BI, Boehringer Ingelheim; BW, body weight; MASLD, metabolic dysfunction-associated steatotic liver disease; mix, mixture within same injection, NW, normal weight; O, obesity; OD, once daily; OW, overweight; QM, once monthly; QW, once weekly; SC, s.c. injection; RA, receptor agonist; Ri, receptor inhibitor; rrLFC, relative reduction in liver fat content; T2D, type 2 diabetes; ↓, decrease

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The concept of continuous slow-release delivery of a GLP-1RA has been assessed in a trial of the Intarcia ITCA 650. This subcutaneously implanted titanium osmotic mini-pump released exenatide and reduced HbA_{1c} by ~13 mmol/mol (1.2%) over 39 weeks compared with placebo in participants with type 2 diabetes; however, the device has not been approved by the US Food and Drug Administration (FDA) [42]. Various biodegradable and low- or non-immunogenic subcutaneous depots have undergone preclinical testing for slow release of GLP-1 and GLP-1 analogues, including microspheres and nanoparticles of poly-lactide-glycolide (PLGA) and modified hydrogel reservoirs [43]. Linkage of GLP-1 into elastin-like protein (ELP) polymers that form viscous reservoirs at body temperature and methods for enzyme-controlled release of GLP-1 from reservoirs have also been described but have yet to receive clinical evaluation [44]. Regarding non-invasive delivery of peptide GLP-1RAs, formulation for oral administration using the absorption enhancer sodium caprylate (SNAC) to facilitate uptake of semaglutide by the stomach is well established, and inhaled and transdermal patch delivery systems are also being tested [45, 46].

Looking beyond GLP-1 receptor mono-agonists, the design of future incretin-based peptide therapies is destined to provide multifunctional capability, such that a single peptide can interact with several different receptors to create a broad portfolio of effects [37].

GLP-1 receptor agonist cautions

Because use of GLP-1RAs is hampered by gastrointestinal and biliary side effects, various dose escalation strategies and dietary adaptations have been implemented. However, future molecules may be able to alleviate this issue via modified effects on neural pathways controlling gastric emptying. There is a risk of hypoglycaemia with over-aggressive use of combination therapies that include a GLP-1RA, even though the individual agents do not carry this risk. In addition, reduced appetite with use of GLP-1RAs requires attention to adequate intake of vitamins, minerals, protein, fibre and fluids. Rapid lowering of hyperglycaemia has been associated with progression of retinopathy in some studies, and long-term use of incretin therapy may be linked to rare cases of non-arteritic anterior ischaemic optic neuropathy (NAION). Debate regarding management of therapy when targets for weight and blood glucose have been achieved currently favours continuation with a low-dose regimen for most individuals [37].

Loss of muscle mass, especially with rapid weight reduction during GLP-1RA therapy, has prompted studies into the utility of agents that promote muscle growth.

Initial studies have indicated preservation of muscle mass when semaglutide therapy is combined with an anti-growth differentiation factor 8 (GDF8)/anti-myostatin antibody (trevogrumab) or an anti-activin A antibody (garetosmab) [47]. Other activin receptor inhibitors such as the monoclonal antibody bimagrumab are also being considered to preserve muscle mass during use of weight loss treatments [48].

GIP/GLP-1 receptor co-agonists

The incretin hormone glucose-dependent insulinotropic polypeptide (GIP) was not initially adopted as a therapeutic because it loses glucose-lowering efficacy in type 2 diabetes [7, 49]. Potentiation of glucose-induced insulin secretion by GIP is diminished in chronic hyperglycaemic states due at least in part to a decrease in the Gs subtype of the GIP receptor in pancreatic beta cells, and further reasons for concern over GIP as a treatment for type 2 diabetes are that it increases glucagon secretion and adipose deposition [49]. However, delivery of a GIP receptor agonist with a GLP-1RA in approximately physiological proportions results in an additive glucose-lowering and weight-lowering effect [49].

Interactions of GIP with GLP-1

Relevant to GIP–GLP-1 interaction is evidence that GIP receptor gene polymorphisms can alter receptor signalling sufficiently to modify the risk and progression of type 2 diabetes [50]. It is also possible that chronic GIP receptor agonism promotes receptor desensitisation or a biased agonism effect that gives rise to functional suppression of GIP activity and enhanced GLP-1 activity [49, 51]. Indeed, preclinical studies have shown that both agonism and antagonism of GIP receptors can reduce hyperglycaemia and body weight [49, 52]. The agonism–antagonism conundrum with GIP is further complicated by species-specific differences in GIP receptor interactions, which have interfered with the usual extrapolation of preclinical findings into clinical drug development [37, 49, 52].

Despite the GIP conundrum, the first approved GIP receptor/GLP-1 receptor co-agonist tirzepatide has confirmed the efficacy gains of the dual agonism effect: placebo-subtracted decreases in HbA_{1c} >22 mmol/mol (>2%) and body weight >8 kg were achieved during 40 week clinical trials in participants with overweight/obesity and type 2 diabetes [53]. Accordingly, several further synthetic peptides that are GIP receptor/GLP-1 receptor co-agonists are advancing in preclinical and early clinical development; for example, LY3537031 is designed for

subcutaneous injection while VK2735 and NN0519-0130 include both injectable and oral formulations (Table 2) [37].

GIP receptor antagonists

Given the reductions in blood glucose and body weight afforded by GIP receptor antagonists in experimental studies, a bispecific monoclonal anti-human GIP receptor antagonist antibody covalently linked to two GLP-1RAs (maridebart cafraglutide, known as MariTide or AMG133) has been developed as a once-monthly subcutaneous injection [54]. In a Phase 1 trial, three once-monthly injections of 420 mg of maridebart cafraglutide in overweight/obese individuals without diabetes reduced body weight by 14%, and most of the weight loss was maintained for 2–3 months after treatment was discontinued [54]. In a 52 week Phase 2 trial, overweight/obese individuals without diabetes lost 13.7% of their body weight (placebo subtracted) after receiving maridebart cafraglutide (420 mg once monthly), and overweight/obese individuals with diabetes lost 10.6% of their body weight and saw a decrease in HbA_{1c} of ~17 mmol/mol (1.5%, placebo subtracted) after receiving maridebart cafraglutide at the same dose (Table 2) [55]. Other approaches to suppress GIP action (yet to undergo clinical trials) include various GIP receptor antagonist peptides, a small molecule GIP receptor antagonist (SKL-14959) and an anti-GIP monoclonal antibody (HCR-188) [51, 56].

Glucagon receptor agonists

Co-agonist and multi-agonist synthetic incretin-based peptides incorporating GCGR agonism are now advancing in pharmaceutical pipelines. These include the GLP-1 receptor/GCGR co-agonists survodutide [57], pemvidutide [58] and mazdutide [59] as well as GIP receptor/GLP-1 receptor/GCGR triple agonists (e.g. retatrutide and efocipegtrutide) (Table 2) [37]. In view of the blood glucose-raising effect of glucagon, the value of GCGR agonism in these therapies might be questioned. However, several of these agents have already shown substantial glucose-lowering efficacy, and it is likely that increased energy expenditure and weight reduction are conferred by GCGR agonism, while GLP-1 receptor agonism suppresses endogenous glucagon secretion [37]. Some of these agents may provide particular benefits in the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD), as they produce substantial

reductions in liver fat content, and others may be more suited to the treatment of obesity without diabetes [60]. However, the GLP-1 receptor/GIP receptor/GCGR triple agonist retatrutide showed strong glucose-lowering and weight-lowering efficacy (HbA_{1c} reduction of 22.4 mmol/mol [2.01%] at 24 weeks and body weight reduction of 13.9% at 36 weeks, placebo subtracted) during a Phase 2 trial in overweight/obese individuals with type 2 diabetes [61]. The GLP-1 receptor/GIP receptor/GCGR triple agonist efocipegtrutide is presently under investigation in individuals with MASLD, and preclinical accounts of other dual and triple agonists that include GLP-1 receptor and GCGR agonism suggest that clinical studies in individuals with type 2 diabetes will follow [62, 63].

Amylin receptor agonists

The use of non-aggregating amylin analogues to reduce body weight and blood glucose through increased satiety, delayed gastric emptying and suppression of glucagon secretion is illustrated by pramlintide, which has been available in some regions since 2005 as an injectable adjunct to insulin therapy [64]. These effects are centrally mediated via the amylin receptor AMY1 (and to a lesser extent the AMY2 and AMY3 receptors) outside the blood–brain barrier in the area postrema. The current focus of research is on the treatment of obesity with long-acting non-precipitating amylin analogues that provide varying selectivity for the different AMY receptors. Examples of agents receiving initial clinical assessment are eloralintide, petrelintide, amylin 355 and 1213, AZ06234, ZP8396 and MET2331. The interaction of calcitonin with a separate part of the AMY receptors does not appear to be affected by interaction with the amylin analogues [64–66].

A long-acting amylin analogue, cagrilintide, which has an N-terminal C-20 fatty acid chain for albumin binding, has shown strong weight-lowering properties, and once-weekly subcutaneous injection of cagrilintide with semaglutide (CagriSema; each at a dose of 2.4 mg) reduced HbA_{1c} by ~24 mmol/mol (2.2%) and body weight by 15.6% (vs baseline) during a 32 week Phase 2 trial in overweight/obese adults with type 2 diabetes [67]. In two Phase 3 studies, a fixed-dose combination of cagrilintide and semaglutide (each at 2.4 mg) was associated with weight reductions of 20.4% and 10.4% (placebo subtracted) after once-weekly subcutaneous injection for 68 weeks in overweight/obese individuals without and with type 2 diabetes, respectively (Table 2) [68].

The activation of AMY and GLP-1 receptors has been further evaluated in preclinical studies using single peptide AMY receptor/GLP-1 receptor co-agonists and in a clinical study with the co-agonist amycretin [64]. When amycretin (50 mg) was delivered as an oral formulation using the gastric absorption enhancer SNAC during a 12 week Phase 1 trial in individuals with obesity, body weight was reduced by 13.1%, boding well for longer-term efficacy [69].

Because AMY receptors also interact with calcitonin, dual amylin/calcitonin receptor agonists (DACRAs) have been developed, with preclinical studies finding greater weight loss than with amylin analogues alone, and additional efficacy in combination with a GLP-1RA [70]. Multi-agonist peptides that incorporate AMY receptor agonism have also been developed as illustrated by PTT-A, a long-acting tetra-agonist at the GLP-1, GIP, amylin and calcitonin receptors that decreased food intake and body weight in a rat model of obesity [71].

Further peptides under investigation

In addition to the receptor agonists described above, several other peptide analogues are receiving preclinical evaluation as potential glucose-lowering and weight-lowering therapies. Examples include peptide tyrosine tyrosine (PYY), pancreatic polypeptide, cholecystokinin (CCK), GLP-2 and secretin, which suppress food intake, mostly via centrally mediated mechanisms [72–76]. Ghrelin receptor antagonists, modulators of neuropeptide Y receptors and activators of neurokinin-2 receptors have also received attention as appetite suppressants and promoters of energy expenditure [74, 74, 77]. The potential importance of assessing peptides from the intestinal tract, in particular, is illustrated by the fact that surgical procedures that bypass, damage or prevent nutrient contact with the duodenal mucosa are all known to improve blood glucose and body weight control in type 2 diabetes [37].

Administration of fibroblast growth factor-21 (FGF21) and analogues and antibodies that exhibit agonism of the fibroblast growth factor receptor 1 (FGFR1)–Klotho beta (KLB) receptor complex can reduce body weight, liver fat, insulin resistance and blood glucose in animal models of obesity and diabetes, and initial clinical studies have encouraged further interest [77]. Fusion proteins linking GLP-1 and FGF21 analogues have shown efficacy in treating MASLD. Although previous trials of leptin receptor (LepR) agonists have failed because of leptin resistance, a LepR/GLP-1 receptor co-agonist has undergone preclinical study [78]. Preclinical assessments of other novel co-agonists that incorporate GLP-1 receptor agonism, include a GLP-1 receptor/CCK receptor co-agonist and a GLP-1 receptor/gastrin receptor co-agonist [79, 80].

Gliprons

Small molecule GLP-1RAs ('gliprons') have been studied in vitro and after oral dosing in animal models, but few have progressed in clinical development due to limitations of potency and possible adverse liver effects (Table 2) [81, 82]. Of note, however, in a 40 week Phase 3 study of overweight/obese individuals with type 2 diabetes, 36 mg of orforglipron taken orally once daily achieved reductions in HbA_{1c} of ~12 mmol/mol (1.07%) and in body weight of 5.9 kg (placebo subtracted) with an adverse event profile similar to that of the established GLP-1RA class [83]. Several oral small molecule GLP-1RAs are presently in early clinical development, including CX11 (VCT220), HRS-7535 and CT-996; the last has shown biased agonism with reduced β -arrestin-mediated receptor internalisation in preclinical studies [84–86]. Small molecule positive allosteric modulators of the GLP-1 receptor, with or without their own agonist capability, can alter the conformation of the GLP-1 receptor and increase its affinity for GLP-1. Whether allosteric receptor modulators could be exploited for therapeutic gain awaits further study [81, 87].

Insulin action enhancers

Although insulin resistance is an underlying feature of most presentations of type 2 diabetes, it may involve multiple defects, which complicates therapeutic targeting, and may extend beyond nutrient metabolism to include vascular activities, growth, electrolyte control and other physiological functions. Potential therapeutic approaches have included activating or prolonging activation of the insulin receptor, promoting signalling through post-receptor pathways and increasing the activity of biological effectors. However, rate-limiting signalling 'bottlenecks' and negative feedback associated with more distal steps in the pathways have diminished the ability of otherwise promising interventions to mimic or enhance early steps in the insulin signalling pathways. In consequence, clinical exploitation of attractive research has been frustrated as described in ESM Appendix 3.

SGLT inhibitors

Sodium–glucose cotransporter (SGLT) 2 inhibitors reduce glucotoxicity by inhibiting renal glucose reabsorption and also provide cardiorenal protective effects. Four SGLT2 inhibitors are currently available in Europe and North America; several others are available in other regions and

others are in development. Some of these agents can also slow intestinal glucose absorption through a modest inhibitory effect on SGLT1, and balanced dual SGLT1/2 inhibitors such as sotagliflozin have been developed that have metabolic and cardiorenal benefits [88]. The cardiorenal protection conferred through SGLT2 and SGLT1/2 inhibition favours use in combination with other classes of glucose-lowering agents.

Preclinical studies have raised interest in developing inhibitors of other types of SGLTs. Attention has focused on inhibition of SGLT4 (in intestine and kidney) and particularly SGLT5 (in kidney) to reduce intake and increase elimination of fructose [89]. It is anticipated that this will improve insulin sensitivity and reduce fatty liver disease, hyperglycaemia and salt-sensitive hypertension.

Other putative glucose-lowering therapies

Insights from genomics, particularly the many genetic variants associated with type 2 diabetes, and from metabolomics and bioinformatics have indicated further potential therapeutic targets, but as yet these have not led to specific pharmacological interventions [90]. Several adipokines with effects on insulin action, energy metabolism or appetite control have been studied, but none has succeeded beyond initial clinical trials (ESM Appendix 3). Lessons learned from other preliminary or unsuccessful interventions are also considered in ESM Appendix 3, including modulators of miRNAs, selective peroxisome proliferator-activated receptor modulators, hydroxysteroid dehydrogenase-1 inhibitors, adenosine monophosphate-activated protein kinase activators, direct modulators of glucose metabolism, regulators of diacylglycerol acyltransferase, sirtuins, selective androgen receptor modulators and agents to modify the microbiome.

Conclusion

Glycaemic control is a fundamental pillar in the management of type 2 diabetes; however, although several classes of glucose-lowering agents are available to address different aspects of disease pathophysiology, many individuals with type 2 diabetes do not achieve or maintain adequate control. The virtues of weight management are also well recognised, and multi-agonist incretin-based and amylin-based synthetic peptides are addressing unmet needs, particularly regarding weight control and beta cell function. Using injections (weekly/monthly) or tablet formulations (daily), these peptides enable simultaneous engagement of several targets, conferring benefits against metabolic

defects plus cardiorenal diseases, fatty liver, cravings and other complications commonly associated with type 2 diabetes. However, achievements of incretin-based therapies are often tempered by the need to maintain lifestyle changes and by gastrointestinal disturbances that compromise dose escalation, tolerability and adherence, indicating challenges for the design of future agents. In addition, although large-scale peptide production is facilitated by solid-state synthesis procedures, high costs are inevitably reflected in high prices for patients. Small molecules that substitute for peptides at receptor targets are emerging in pharmaceutical pipelines, assisted in design by advanced imaging technologies. Small molecules raise the prospect of less expensive medicines, but (unlike multi-agonist peptides) require a different molecule to interact with each type of receptor, suggesting that fixed-dose combination tablets may become more fashionable to service multi-drug strategies. Of note for drug development programmes is that guidelines and regulatory agencies are placing ever stronger emphasis on the delivery of benefits beyond glycaemic control, particularly weight control and cardiorenal protection, and on predicting best responders as part of the quest for precision medicine.

Many promising preclinical approaches to preserve beta cells, relieve insulin signalling ‘pinch points’ or directly modify intermediary metabolism have been stalled by unwanted off-target effects and have not proceeded through clinical development. New technologies including miRNAs, epigenetic modulators and artificial intelligence-guided compound design are in their infancy and have yet to supply agents to fill treatment gaps, and agents to drive beta cell neogenesis are a distant (but not unrealistic) prospect. Future attention to disease prevention could accommodate approaches beyond conventional glucose and weight control that consider how inflammatory, infective and environmental stress factors contribute to type 2 diabetes. In addition, with early diagnosis comes the opportunity for prompt use of agents to assist at least with temporary remission and defer complications; however, a permanent cure is not in sight. In the meantime, it is timely to reinforce the message in guidelines to use currently available medicines as effectively as possible to counter the ever-present challenge of ‘hyperglycaemia + time = complications’.

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References

- Bailey CJ, Day C (2018) Treatment of type 2 diabetes: future approaches. *Br Med Bull* 126:123–137. <https://doi.org/10.1093/brimed/ldy013>
- American Diabetes Association Professional Practice Committee (2025) Standards of care in diabetes 2025. *Diabetes Care* 48(Suppl 1):S1–S352
- Davies MJ, Aroda VR, Collins BS et al (2022) Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 65:1925–1966. <https://doi.org/10.1007/s00125-022-05787-2>
- Samson SL, Vellanki P, Blonde L et al (2023) American association of clinical endocrinology consensus statement: comprehensive type 2 diabetes management algorithm – 2023 update. *Endocr Pract* 29:305–340. <https://doi.org/10.1016/j.eprac.2023.02.001>
- Bailey CJ (2022) The origins of type 2 diabetes medications. *Br J Diabetes* 22:112–120. <https://doi.org/10.15277/bjd.2022.388>
- Kahn SE, Cooper ME, Del Prato S (2014) Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present and future. *Lancet* 383:1068–1083. [https://doi.org/10.1016/S0140-6736\(13\)62154-6](https://doi.org/10.1016/S0140-6736(13)62154-6)
- Nauck MA, Müller TD (2023) Incretin hormones and type 2 diabetes. *Diabetologia* 66:1780–1795. <https://doi.org/10.1007/s00125-023-05956-x>
- Blonde L, Aschner P, Bailey C, Ji L, Leiter LA, Matthei S (2017) Global Partnership for Effective Diabetes Management: Gaps and barriers in the control of blood glucose in people with type 2 diabetes. *Diab Vasc Dis Res* 14:172–183. <https://doi.org/10.1177/1479164116679775>
- Bailey CJ (2024) Future drug treatments for type 2 diabetes. In: Holt RIG, Flyvbjerg A (eds) *Textbook of diabetes*, 6th edn. Wiley, Chichester, UK, pp 1154–1166
- US Food and Drug Administration (2020) Type 2 diabetes mellitus: evaluating the safety of new drugs for improving glycemic control guidance for industry. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/type-2-diabetes-mellitus-evaluating-safety-new-drugs-improving-glycemic-control-guidance-industry>. Accessed: 10 Jun 2025
- European Medicines Agency (2023) Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-or-prevention-diabetes-mellitus-revision-2_en.pdf. Accessed: 10 Jun 2025
- Congressional Budget Office (2021) Research and development in the pharmaceutical industry. Available from: <https://www.cbo.gov/publication/57126>. Accessed: 10 Jun 2025
- Eizirik DL, Pasquali L, Cnop M (2020) Pancreatic β -cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nat Rev Endocrinol* 16:349–362. <https://doi.org/10.1038/s41574-020-0355-7>
- Singh AK, Singh A, Singh R, Misra A (2023) Efficacy and safety of imeglimin in type 2 diabetes: A systematic review and meta-analysis of randomized placebo-controlled trials. *Diabetes Metab Syndr* 17:102710. <https://doi.org/10.1016/j.dsx.2023.102710>
- Hallakou-Bozec S, Kergoat M, Fouqueray P, Bolze S, Moller DE (2021) Imeglimin amplifies glucose-stimulated insulin release from diabetic islets via a distinct mechanism of action. *PLoS ONE* 16:e0241651. <https://doi.org/10.1371/journal.pone.0241651>
- Hozumi K, Sugawara K, Ishihara T et al (2023) Effects of imeglimin on mitochondrial function, AMPK activity, and gene expression in hepatocytes. *Sci Rep* 13:746. <https://doi.org/10.1038/s41598-023-27689-y>
- Aoyagi K, Nishiwaki C, Nakamichi Y et al (2024) Imeglimin mitigates the accumulation of dysfunctional mitochondria to restore insulin secretion and suppress apoptosis of pancreatic β -cells from db/db mice. *Sci Rep* 14:6178. <https://doi.org/10.1038/s41598-024-56769-w>
- Hou T, Zhang J, Shi W (2025) Mechanisms and clinical perspectives on imeglimin for insulin resistance in obese patients. *Eur J Pharmacol* 1003:177937. <https://doi.org/10.1016/j.ejphar.2025.177937>
- Thilagavathi R, Hosseini-Zare MS, Malini M, Selvam C (2022) A comprehensive review on glucokinase activators: Promising agents for the treatment of Type 2 diabetes. *Chem Biol Drug Des* 99(2):247–263. <https://doi.org/10.1111/cbdd.13979>
- Ashcroft FM, Lloyd M, Haythorne EA (2023) Glucokinase activity in diabetes: too much of a good thing? *Trends Endocrinol Metab* 34:119–130. <https://doi.org/10.1016/j.tem.2022.12.007>
- Haddad D, Dsouza VS, Al-Mulla F, Al Madhoun A (2024) New-generation glucokinase activators: potential game-changers in type 2 diabetes treatment. *Int J Mol Sci* 25:571. <https://doi.org/10.3390/ijms25010571>
- Zhu D, Li X, Ma J, Zeng J et al (2022) Dorzagliatin in drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med* 28:965–973. <https://doi.org/10.1038/s41591-022-01802-6>
- Jiang Y, Wang L, Dong Z, Xia B, Pang S (2024) Recent drug development of dorzagliatin, a new glucokinase activator, with the potential to treat Type 2 diabetes: a review study. *J Diabetes* 16:e13563. <https://doi.org/10.1111/1753-0407.13563>
- Lis J, Fichna J, Tarasiuk-Zawadzka A (2025) The role of free fatty acid receptors activation in pancreatic disorders. *Mol Asp Med* 104:101386. <https://doi.org/10.1016/j.mam.2025.101386>
- Hryciw DH, Patten RK, Rodgers RJ, Proietto J, Hutchinson DS, McAinch AJ (2024) GPR119 agonists for type 2 diabetes: past failures and future hopes for preclinical and early phase candidates. *Expert Opin Investig Drugs* 33:183–190. <https://doi.org/10.1080/13543784.2024.2321271>
- Yoon J, Lee DG, Song H et al (2024) Xelaglifam, a novel GPR40/FFAR1 agonist, exhibits enhanced β -arrestin recruitment and sustained glycemic control for type 2 diabetes. *Biomed Pharmacother* 177:117044. <https://doi.org/10.1016/j.biopha.2024.117044>

27. Carr ER, Higgins PB, McClenaghan NH, Flatt PR, McCloskey AG (2024) MicroRNA regulation of islet and enteroendocrine peptides: physiology and therapeutic implications for type 2 diabetes. *Peptides* 176:171196. <https://doi.org/10.1016/j.peptides.2024.171196>
28. Ofori JK, Karagiannopoulos A, Nagao M et al (2022) Human islet microRNA-200c is elevated in type 2 diabetes and targets the transcription factor ETV5 to reduce insulin secretion. *Diabetes* 71:275–284. <https://doi.org/10.2337/db21-0077>
29. Seyhan AA (2024) Trials and tribulations of microRNA therapeutics. *Int J Mol Sci* 25:1469. <https://doi.org/10.3390/ijms25031469>
30. Su K, Xu J, Hu S, Ye H, Xie L, Ouyang S (2024) Advances in small-molecule insulin secretagogues for diabetes treatment. *Biomed Pharmacother* 178:117179. <https://doi.org/10.1016/j.biopha.2024.117179>
31. Álvarez-Cubela S, Altilio ID, Doke M et al (2025) Pancreatic β -cell regeneration in situ by the ALK3 agonist THR-123. *Nat Commun* 16:6121. <https://doi.org/10.1038/s41467-025-61534-2>
32. Son J, Accili D (2023) Reversing pancreatic β -cell dedifferentiation in the treatment of type 2 diabetes. *Exp Mol Med* 55:1652–1658. <https://doi.org/10.1038/s12276-023-01043-8>
33. Wu J, Li T, Guo M et al (2024) Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue. *Cell Discov* 10:45. <https://doi.org/10.1038/s41421-024-00662-3>
34. Raoufinia R, Rahimi HR, Saburi E et al (2024) Advances and challenges of the cell-based therapies among diabetic patients. *J Transl Med* 22:435. <https://doi.org/10.1186/s12967-024-05226-3>
35. Hædersdal S, Lund A, Knop FK, Vilsbøll T (2018) The role of glucagon in the pathophysiology and treatment of type 2 diabetes. *Mayo Clin Proc* 93:217–239. <https://doi.org/10.1016/j.mayocp.2017.12.003>
36. Sammons MF, Lee ECY (2015) Recent progress in the development of small-molecule glucagon receptor antagonists. *Bioorg Med Chem Lett* 25:4057–4064. <https://doi.org/10.1016/j.bmcl.2015.07.092>
37. Bailey CJ, Flatt PR, Conlon JM (2025) Multifunctional incretin peptides in therapies for type 2 diabetes, obesity and associated co-morbidities. *Peptides* 187:171380. <https://doi.org/10.1016/j.peptides.2025.171380>
38. Narayan N, Vadde T, Sandesara M, Divity S, Mamytova A, Tagaev T (2025) Efficacy and safety of epeglenatide in patients with type 2 diabetes and obesity: a systematic review. *Cureus* 17:e77089. <https://doi.org/10.7759/cureus.77089>
39. Del Prato S, Kang J, Trautmann ME et al (2020) Efficacy and safety of once-monthly epeglenatide in patients with type 2 diabetes: results of a phase 2 placebo-controlled, 16-week randomized dose-finding study. *Diabetes Obes Metab* 22:1176–1186. <https://doi.org/10.1111/dom.14020>
40. Zhou H, Ji L, Song X et al (2024) ZT002, a novel ultra long-acting GLP-1 receptor agonist in adults with overweight or obesity: a randomised, placebo-controlled, multiple ascending dose phase 1c study. *Diabetologia* 67(Suppl 1): abstract 147
41. Zhu D, Wang W, Tong G et al (2024) Efficacy and safety of GLP-1 analog ecnoglutide in adults with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 2 trial. *Nat Commun* 15:8408. <https://doi.org/10.1038/s41467-024-52353-y>
42. Rosenstock J, Buse JB, Azeem R (2018) Efficacy and Safety of ITCA 650, a novel drug-device GLP-1 receptor agonist, in type 2 diabetes uncontrolled with oral antidiabetes drugs: the FREEDOM-1 trial. *Diabetes Care* 41:333–340. <https://doi.org/10.2337/dc17-1306>
43. d'Aquino AI, Maikawa CL, Nguyen LT (2023) Use of a biomimetic hydrogel depot technology for sustained delivery of GLP-1 receptor agonists reduces burden of diabetes management. *Cell Rep Med* 4:101292. <https://doi.org/10.1016/j.xcrm.2023.101292>
44. Amiram M, Luginbuhl KM, Li X, Feinglos MN, Chilkoti A (2013) A depot-forming glucagon-like peptide-1 fusion protein reduces blood glucose for five days with a single injection. *J Control Release* 172:144–151. <https://doi.org/10.1016/j.jconrel.2013.07.021>
45. Babenko M, Alany RG, Calabrese G, Kaialy W, ElShaer A (2022) Development of drug alone and carrier-based GLP-1 dry powder inhaler formulations. *Int J Pharmaceutics* 617:121601. <https://doi.org/10.1016/j.ijpharm.2022.121601>
46. Li W, Cai R, Yin B, Zhou Y, Dong X, Li W, Wen J (2025) Transdermal semaglutide administration in mice: reduces body weight by suppressing appetite and enhancing metabolic rate. *Biology (Basel)* 14:575. <https://doi.org/10.3390/biology14050575>
47. Regeneron (2025) Results from Phase 2 COURAGE trial demonstrating potential to improve quality of GLP-1 receptor agonist-induced weight loss by preserving lean mass. Press release. Available from: <https://investor.regeneron.com/news-releases/news-release-details/results-phase-2-courage-trial-demonstrating-potential-improve>. Accessed: 25 Sep 2025
48. Heymsfield SB, Coleman LA, Müller R et al (2021) Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw Open* 4:e2033457. <https://doi.org/10.1001/jamanetworkopen.2020.33457>. Erratum 4: e212581.
49. Müller TD, Adriaenssens A, Ahren B et al (2025) Glucose-dependent insulinotropic polypeptide (GIP). *Mol Metab* 95:102118. <https://doi.org/10.1016/j.molmet.2025.102118>
50. Barbosa-Yañez RL, Markova M, Dambeck U et al (2020) Predictive effect of GIPR SNP rs10423928 on glucose metabolism liver fat and adiposity in prediabetic and diabetic subjects. *Peptides* 125:170237. <https://doi.org/10.1016/j.peptides.2019.170237>
51. Lafferty RA, Flatt PR, Gault VA, Irwin N (2024) Does glucose-dependent insulinotropic polypeptide receptor blockade as well as agonism have a role to play in management of obesity and diabetes? *J Endocrinology* 262:0339. <https://doi.org/10.1530/JOE-23-0339>
52. Flatt PR (2008) Gastric inhibitory polypeptide (GIP) revisited: a new therapeutic target for obesity-diabetes? *Diabet Med* 25:759–764. <https://doi.org/10.1111/j.1464-5491.2008.02455.x>
53. De Block C, Bailey C, Wysham C, Hemmingway A, Allen SE, Peleshok J (2022) Tirzepatide for the treatment of adults with type 2 diabetes: an endocrine perspective. *Diabetes Obes Metab* 25:3–17. <https://doi.org/10.1111/dom.14831>
54. Véniant MM, Lu SC, Atangan L et al (2024) A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat Metab* 6:290–303. <https://doi.org/10.1038/s42255-023-00966-w>
55. Jastreboff AM, Ryan DH, Bays HE, MariTide phase 2 obesity trial investigators et al (2025) Once-monthly maridebart cafraglutide for the treatment of obesity - a phase 2 trial. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2504214>
56. Nakamura T, Tanimoto H, Mizuno Y et al (2018) Gastric inhibitory polypeptide receptor antagonist, SKL-14959, suppressed body weight gain on diet-induced obesity mice. *Obes Sci Pract* 4:194–203. <https://doi.org/10.1002/osp4.164>
57. le Roux CW, Steen O, Luca KJ, Startseva E, Unsel A, Hennige AM (2024) Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. *Lancet Diabetes Endocrinol* 12:162–173. <https://doi.org/10.1016/S2213-X>
58. Harrison SA, Browne SK, Suschak JJ et al (2025) Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: a randomized, double-blind, placebo-controlled study. *J Hepatol* 82(2025):7–17. <https://doi.org/10.1016/j.jhep.2024.07.006>
59. Zhang B, Cheng Z, Chen J et al (2024) Efficacy and safety of mazdutide in Chinese patients with type 2 diabetes: a randomized,

- double-blind, placebo-controlled phase 2 trial. *Diabetes Care* 47:160–168. <https://doi.org/10.2337/dc23-1287>
60. Targher G, Mantovani A, Byrne CD, Tilg H (2024) Recent advances in incretin-based therapy for MASLD: from single to dual or triple incretin receptor agonists. *Gut* 74:487–497. <https://doi.org/10.1136/gutjnl-2024-334023>
 61. Rosenstock J, Frias J, Jastreboff AM (2023) Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet* 402:529–544. [https://doi.org/10.1016/S0140-6736\(23\)01053-X](https://doi.org/10.1016/S0140-6736(23)01053-X)
 62. Brouwers B, Rao G, Tang Y et al (2024) Incretin-based investigational therapies for the treatment of MASLD/MASH. *Diabetes Res Clin Pract* 211:111675. <https://doi.org/10.1016/j.diabres.2024.111675>
 63. Gutgesell RM, Nogueiras R, Tschöp MH, Müller TD (2024) Dual and triple incretin-based co-agonists: novel therapeutics for obesity and diabetes. *Diabetes Ther* 15:1069–1084. <https://doi.org/10.1007/s13300-024-01566-x>
 64. Walker C, Aitken JF, Amarsingh GV et al (2025) Amylin: emergent therapeutic opportunities in overweight, obesity and diabetes mellitus. *Nat Rev Endocrinol* 21:482–494. <https://doi.org/10.1038/s41574-025-01125-9>
 65. Melson E, Ashraf U, Papamargaritis D, Davies MJ (2025) What is the pipeline for future medications for obesity? *Int J Obes (Lond)* 49:433–451. <https://doi.org/10.1038/s41366-024-01473-y>
 66. Volčanšek Š, Koceva A, Jensterle M, Janež A, Muzurović E (2025) Amylin: from mode of action to future clinical potential in diabetes and obesity. *Diabetes Ther* 16:1207–1227. <https://doi.org/10.1007/s13300-025-01733-8>
 67. Frias JP, Deenadayalan S, Erichsen L (2023) Efficacy and safety of co-administered once-weekly cagrilintide 2.4 mg with once-weekly semaglutide 2.4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet* 402:720–730. [https://doi.org/10.1016/S0140-6736\(23\)01163-7](https://doi.org/10.1016/S0140-6736(23)01163-7)
 68. Davies MJ, Bajaj HS, Broholm C et al (2025) Cagrilintide–semaglutide in adults with overweight or obesity and type 2 diabetes. *N Engl J Med* 393:648–659. <https://doi.org/10.1056/NEJMoa2502082>
 69. Gasiorek A, Heydorn A, Gabery S et al (2025) Safety, tolerability, pharmacokinetics, and pharmacodynamics of the first-in-class GLP-1 and amylin receptor agonist, amycretin: a first-in-human, phase 1, double-blind, randomised, placebo-controlled trial. *Lancet* 406(10499):135–148. [https://doi.org/10.1016/S0140-6736\(25\)01176-6](https://doi.org/10.1016/S0140-6736(25)01176-6)
 70. Larsen AT, Mohamed KE, Melander SA, Karsdal MA, Henriksen K (2024) The enduring metabolic improvement of combining dual amylin and calcitonin receptor agonist and semaglutide treatments in a rat model of obesity and diabetes. *Am J Physiol Endocrinol Metab* 327:E145–E154. <https://doi.org/10.1152/ajpendo.00092.2024>
 71. Rondinone CM, Valdecantos P, Rada P, Valverde AM, Ghosh S (2024) Novel unimolecular tetra-agonist peptides targeting GLP-1, GIP, amylin, and calcitonin receptors with enhanced metabolic benefits in animal models of obesity. *Diabetologia* 67(Suppl 1):abstract 81
 72. Ali A, Khan D, Dubey V, Tarasov AI, Flatt PR, Irwin N (2024) Comparative effects of GLP-1 and GLP-2 on beta-cell function, glucose homeostasis and appetite regulation. *Biomolecules* 14:1520. <https://doi.org/10.3390/biom14121520>
 73. Lafferty RA, Flatt PR, Irwin N (2024) NPYR modulation: potential for the next major advance in obesity and type 2 diabetes management? *Peptides* 179:171256. <https://doi.org/10.1016/j.peptides.2024.171256>
 74. Rubinić I, Kurtov M, Likić R (2024) Novel pharmaceuticals in appetite regulation: exploring emerging gut peptides and their pharmacological prospects. *Pharmacol Res Perspect* 12:1243. <https://doi.org/10.1002/prp2.1243>
 75. Zhu W, Tanday N, Flatt PR, Irwin N (2023) Pancreatic polypeptide revisited: potential therapeutic effects in obesity–diabetes. *Peptides* 160:170923. <https://doi.org/10.1016/j.peptides.2022.170923>
 76. Warrilow A, Turner M, Naumovski N, Somerset S (2023) Role of cholecystokinin in satiation: a systematic review and meta-analysis. *Br J Nutrition* 129:2182–2190. <https://doi.org/10.1017/S0007114522000381>
 77. Chen Z, Yang L, Liu Y, Huang P, Song H, Zheng P (2022) The potential function and clinical application of FGF21 in metabolic diseases. *Front Pharmacol* 13:1089214. <https://doi.org/10.3389/fphar.2022.1089214>
 78. Poley-Wolf J, Deibler K, Hogendorf WF et al (2024) GIPr-Lepr coexpressing neurons modulate the suppression of food intake and body weight by a GLP-1/leptin dual agonist. *Sci Transl Med* 16:776. <https://doi.org/10.1126/scitranslmed.adk4908>
 79. Zhou F, Song P, Tang X et al (2022) Discovery of once weekly, peptide-based selective GLP-1 and cholecystokinin 2 receptors co-agonists. *Peptides* 153:170811. <https://doi.org/10.1016/j.peptides.2022.170811>
 80. Skarbaliene J, Secher T, Jelsing J et al (2015) The anti-diabetic effects of GLP-1-gastrin dual agonist ZP3022 in ZDF rats. *Peptides* 69:47–55. <https://doi.org/10.1016/j.peptides.2015.03.024>
 81. Zhang H, Wu T, Wu Y et al (2024) Binding sites and design strategies for small molecule GLP-1R agonists. *Eur J Med Chem* 275:116632. <https://doi.org/10.1016/j.ejmech.2024.116632>
 82. Saldívar-Cerón HI, Vargas-Camacho JA, León-Cabrera S et al (2025) Oral small-molecule GLP-1 receptor agonists: mechanistic insights and emerging therapeutic strategies. *Sci Pharm* 93:26. <https://doi.org/10.3390/scipharm93020026>
 83. Rosenstock J, Hsia S, Ruiz LN et al (2025) Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes. *N Engl J Med* 393:1065–1076. <https://doi.org/10.1056/NEJMoa2505669>
 84. Wu J, Zhou R, Zhang Q et al (2024) Safety, pharmacokinetics, and pharmacodynamics of HRS-7535, a novel oral small molecule glucagon-like peptide-1 receptor agonist, in healthy subjects: a phase 1, randomized, double-blind, placebo-controlled, single- and multiple-ascending dose, and food effect trial. *Diabetes Obes Metab* 26(3):901–910. <https://doi.org/10.1111/dom.15383>
 85. Roche (2024) Roche announces positive Phase I results of its oral GLP-1 receptor agonist CT-996 for the treatment of people with obesity. Press release. Available from: <https://www.roche.com/media/releases/med-cor-2024-07-17>. Accessed: 19 Sep 2025
 86. Ji L, Gao L, Meng S, Zhang X, Huang J, Li B (2025) Efficacy and safety of VCT220 in Chinese adults with overweight or obesity. *Diabetes* 74(Suppl 1):743-P. <https://doi.org/10.2337/db25-743-P>
 87. Malik F, Li Z (2022) Non-peptide agonists and positive allosteric modulators of glucagon-like peptide-1 receptors: Alternative approaches for treatment of Type 2 diabetes. *Br J Pharmacol* 179:511–525. <https://doi.org/10.1111/bph.15446>
 88. Fatima E, Irfan H, Fatima F (2025) Is sotagliflozin a ‘wonder drug’? A review of its impact on cardiovascular, diabetic, renal, neuroprotective, and hepatic outcomes. *Ann Med Surg (Lond)* 87:3700–3706. <https://doi.org/10.1097/MS9.0000000000003357>
 89. Siddiqui SH, Rossi NF (2025) High-fructose-induced salt-sensitive hypertension: the potential benefit of SGLT4 or SGLT5 modulation. *Nutrients* 17(15):2511. <https://doi.org/10.3390/nu17152511>
 90. Cheng C, Liu Y, Sun L et al (2025) Integrative metabolomics and genomics reveal molecular signatures for type 2 diabetes and its cardiovascular complications. *Cardiovasc Diabetol* 24:166. <https://doi.org/10.1186/s12933-025-02718-4>

91. Roche (2024) Roche reports positive Phase Ib results for its dual GLP-1/GIP receptor agonist CT-388 in people with obesity. Press release. Available from: <https://www.roche.com/media/releases/med-cor-2024-05-16>. Accessed: 19 Sep 2025
92. Jastreboff AM, Kaplan LM, Frias JP et al (2023) Triple-hormone-receptor agonist retatrutide for obesity: a phase 2 trial. *N Engl J Med* 389:514–526. <https://doi.org/10.1056/NEJMoa2301972>
93. Sanyal AJ, Kaplan LM, Frias JP et al (2024) Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat Med* 30:2037–2048. <https://doi.org/10.1038/s41591-024-03018-2>
94. Viking Therapeutics (n.d.) VK2735 (subcutaneous & oral formulations) dual GLP-1/GIP receptor agonist. Available from: <https://vikingtherapeutics.com/pipeline/metabolic-disease-program/vk2735/>. Accessed: 19 Sep 2025
95. Viking Therapeutics (2025) Viking Therapeutics announces positive top-line results from phase 2 VENTURE-oral dosing trial of VK2735 tablet formulation in patients with obesity. Press release. Available from: <https://www.prnewswire.com/news-releases/viking-therapeutics-announces-positive-top-line-results-from-phase-2-venture-oral-dosing-trial-of-vk2735-tablet-formulation-in-patients-with-obesity-302533355.html>. Accessed: 19 Sep 2025
96. Frias JP, Hsia S, Eyde S et al (2023) Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *Lancet* 402(10400):472–483. [https://doi.org/10.1016/S0140-6736\(23\)01302-8](https://doi.org/10.1016/S0140-6736(23)01302-8)
97. Structure Therapeutics (2025) Structure Therapeutics reports second quarter 2025 financial results and recent highlights. Press release. Available from: <https://ir.structuretx.com/news-releases/news-release-details/structure-therapeutics-reports-second-quarter-2025-financial>. Accessed: 19 Sep 2025
98. Nelson CH, Jones C, Kwan E, Castelloe EN, Marmon T, Kuria-kose ET (2025) Effect of oral small molecule GLP-1 receptor agonist TERN-601 in healthy participants with obesity or overweight—a first-in-human study. *Diabetes* 74(Suppl 1):307-OR. <https://doi.org/10.2337/db25-307-OR>
99. Bailey CJ, Tahrani AA, Barnett AH (2016) Future glucose-lowering drugs for type 2 diabetes. *Lancet Diabetes Endocrinol* 4:350–359. [https://doi.org/10.1016/S2213-8587\(15\)00462-3](https://doi.org/10.1016/S2213-8587(15)00462-3)

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