

Future therapies for obesity

Authors: Eka Melson,^A Alexander Dimitri Miras^B and Dimitris Papamargaritis^C

ABSTRACT

Obesity is a chronic disease associated with increased morbidity and mortality. Bariatric surgery can lead to sustained long-term weight loss (WL) and improvement in multiple obesity-related complications, but it is not scalable at the population level. Over the past few years, gut hormone-based pharmacotherapies for obesity and type 2 diabetes mellitus (T2DM) have rapidly evolved, and combinations of glucagon-like peptide 1 (GLP1) with other gut hormones (glucose-dependent insulinotropic polypeptide (GIP), glucagon, and amylin) as dual or triple agonists are under investigation to enhance and complement the effects of GLP1 on WL and obesity-related complications. Tirzepatide, a dual agonist of GLP1 and GIP receptors, marks a new era in obesity pharmacotherapy in which a combination of gut hormones could approach the WL achieved with bariatric surgery. In this review, we discuss emerging obesity treatments with a focus on gut hormone combinations and the concept of a multimodal approach for obesity management.

KEYWORDS: obesity, pharmacotherapy, tirzepatide, gut hormones

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Introduction

Obesity is a complex, chronic disease associated with increased morbidity and mortality, and affects 28% of the UK population.^{1,2} The aim of obesity treatment is to improve health and quality of life through sustained weight loss (WL).³

Lifestyle interventions are the first-line treatment for obesity; however, even the most intensive lifestyle interventions usually result in only a 5–10% WL and weight maintenance over time remains challenging because of compensatory physiological mechanisms resulting in increased appetite and reduced energy expenditure.⁴ Although 5–10% WL is clinically meaningful, greater WL (10–25%) might be required,

especially in people with a body mass index (BMI) ≥ 35 kg/m², to improve or achieve remission of certain obesity-related complications and reduce risk for cardiovascular events.^{3,5} If individualised WL targets cannot be achieved through lifestyle interventions, the next option is to add pharmacotherapy or progress to bariatric surgery, if eligible. Bariatric surgery can result in $\geq 25\%$ WL and long-term weight maintenance (Fig 1), but it is not scalable at the population level and many people remain apprehensive about undertaking surgery given the risk of complications, when other candidates might not be fit enough for anaesthesia.^{6,7}

A better understanding of the complex physiology of weight regulation, and the role of gut hormones in the regulation of feeding, appetite and glucose homeostasis, has led to the discovery of glucagon-like peptide 1 (GLP1) receptor analogues (RAs) as safe and effective therapeutics initially for type 2 diabetes mellitus (T2DM) and, over the past few years, in higher doses for the treatment of obesity (liraglutide 3 mg and semaglutide 2.4 mg).^{8,9} GLP1 is a hormone secreted mainly from the ileum and results in reduced appetite, delayed gastric emptying, increased insulin secretion and inhibition of glucagon secretion (Fig 2).¹⁰ In 2021, semaglutide 2.4 mg once weekly, a new GLP1 RA, became the first treatment approved for obesity, resulting in a mean WL of ~15% and maintenance through appetite reduction.^{11,12} However, there is still a marked difference to the WL achieved with bariatric surgery, the response to semaglutide 2.4 mg once weekly can be limited in some populations (32% of people with T2DM will achieve $\leq 5\%$ WL with semaglutide 2.4 mg), the adverse events with GLP1 RAs are generally dose dependent and some people are adverse to injectable treatments.^{13,14}

In this review, we discuss emerging pharmacotherapies for obesity and those in the drug discovery pipeline, with a main focus on gut hormone combinations.

Oral GLP1 RAs

Oral semaglutide is approved for T2DM at doses up to 14 mg once daily and provides an additional option for people reluctant to initiate injectable treatments.¹⁵ A press release of the results of the phase III PIONEER-PLUS trial revealed that 50 mg oral semaglutide daily in people with T2DM resulted in 8 kg WL compared with 4.4 kg WL with 14 mg oral semaglutide.¹⁶ Mild-to-moderate gastrointestinal symptoms were the most commonly reported adverse effects. Currently, a phase III trial in people with obesity (without diabetes) is investigating the safety and efficacy on WL of oral semaglutide 50 mg daily (NCT05035095).

Authors: ^ANIHR academic clinical fellow in diabetes and endocrinology, Diabetes Research Centre, Leicester General Hospital, University of Leicester, Leicester, UK; ^Bprofessor of endocrinology, School of Medicine, University of Ulster, Ulster, UK; ^Cconsultant in diabetes and endocrinology, Kettering General Hospital NHS Foundation Trust, Kettering, UK and associate professor in diabetes and endocrinology, Diabetes Research Centre, Leicester General Hospital, University of Leicester, Leicester, UK

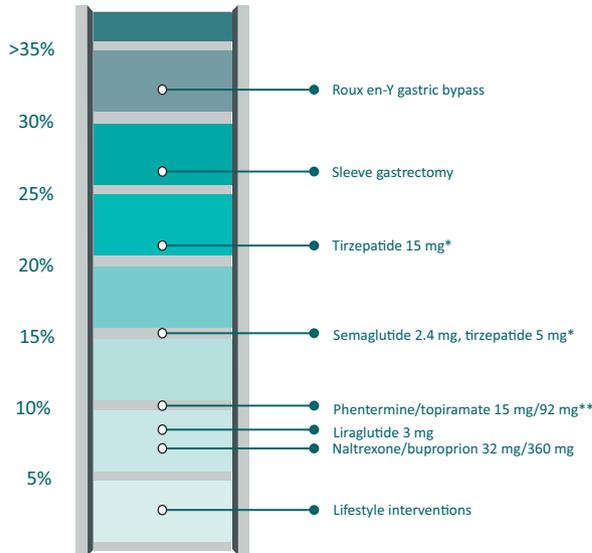


Fig 1. The mean weight loss achieved at approximately 1 year follow-up with moderate-intensity lifestyle interventions (500 kcal/day deficit diet and advice to exercise for 150 min/week), currently available pharmacotherapies (and tirzepatide) and bariatric surgery in people without diabetes. *Not approved yet for obesity management; **approved in the USA, but not in Europe.

resulted in a placebo-adjusted WL of 5.5% after 28 days in people with T2DM and obesity and it was well tolerated.¹⁷

Combination of gut hormones

The concept of combining gut hormones for obesity management originates from the remarkable results of bariatric surgery on WL, weight maintenance and obesity-related complications, an intervention leading to enhanced levels of multiple gut hormones.^{18,19} In the search for the next generation of obesity pharmacotherapies, numerous molecules with diverse metabolic actions are under investigation in combination with GLP1 RAs (glucose-dependent insulinotropic polypeptide (GIP), glucagon, amylin and peptide YY agonists, and GIP antagonists) aiming to enhance and complement the effect of GLP1 agonism on weight and metabolism through different mechanisms of actions (Fig 2). Indeed, the therapeutic potential of combining multiple gut hormones is supported by preclinical studies and early-phase clinical trial data.²⁰

Emerging pharmacotherapies for obesity

Dual-agonism GLP1 and GIP

GIP is a hormone secreted from the jejunum in response to food intake. It stimulates insulin secretion, increases glucagon secretion and the lipid-buffering capacity of the adipose tissue.^{20,21} In preclinical models, simultaneous activation of GLP1 and GIP receptors resulted in greater WL and glucose-lowering efficacy compared with activation of each receptor alone and this

Danuglipron is another oral GLP1 RA currently under development (NCT04707313). In early-phase clinical studies, 120 mg twice daily

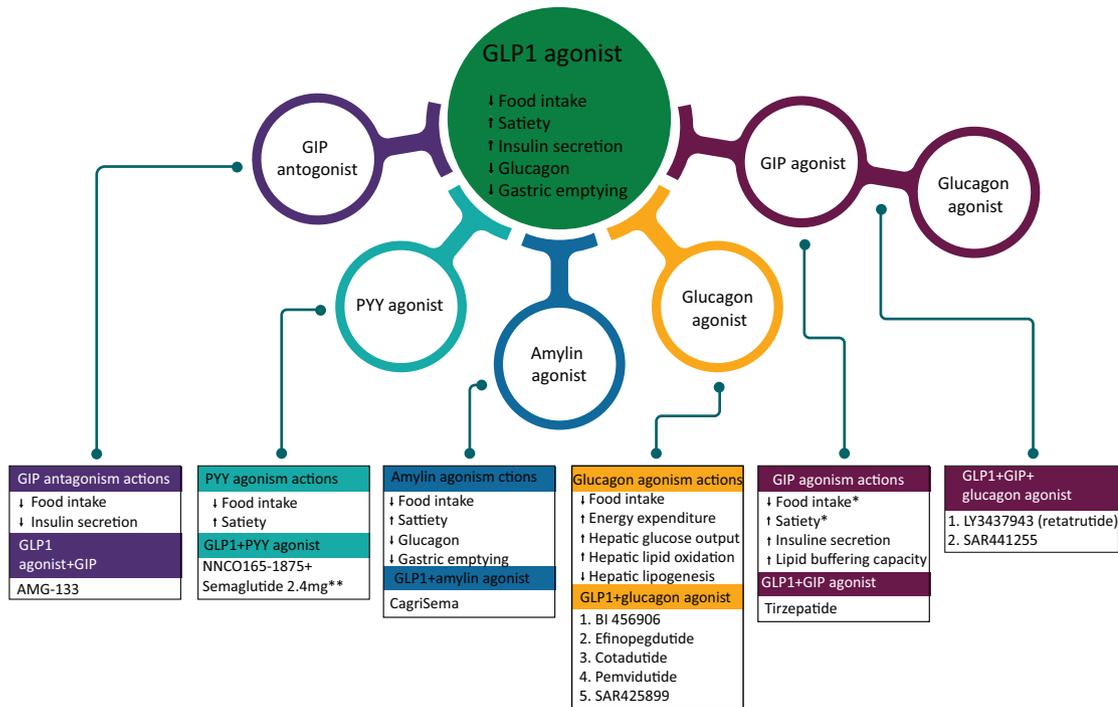


Fig 2. Pharmacotherapies under investigation based on a combination of glucagon-like peptide 1 (GLP1) with other gut hormones and the actions related to agonism of each gut hormone and antagonism of glucose-dependent insulinotropic polypeptide (GIP). PYY = Peptide YY; *action in preclinical models; **clinical data not available yet.

increased interest in the development of unimolecular agonists of GLP1 and GIP receptors.^{20,22,23}

Tirzepatide

Tirzepatide was the first dual GLP1 and GIP receptor agonist approved for T2DM management (5 mg, 10 mg and 15 mg doses, once weekly subcutaneous) based on the SURPASS programme findings (Table 1).¹⁸ Mean glycated haemoglobin (HbA1c) reduction ranged between 1.87% and 2.59% with the different tirzepatide doses and 62–86% of patients achieved HbA1c \leq 6.5%. WL with the highest doses of tirzepatide (10–15 mg) ranged between 9.5 kg and 12.9 kg with 40–69% of patients achieving \geq 10% WL, even though there was no additional support for lifestyle intervention as part of the SURPASS programme (Table 1).¹⁸ Tirzepatide was more efficacious both for glycaemic improvement and WL compared with placebo and other glucose-lowering agents, including semaglutide 1 mg.^{24–28} In people with T2DM, tirzepatide 15 mg improved insulin secretion and insulin sensitivity more compared with semaglutide 1 mg and placebo, and reduced food intake and appetite compared with placebo.^{29,30}

Tirzepatide has not yet been approved for obesity management; however, a large phase III clinical trial (SURMOUNT-1) in people with obesity (without diabetes) assessed the safety and efficacy of tirzepatide 5, 10 and 15 mg once weekly versus placebo when combined with a 500 kcal/day deficit diet and advice to exercise for 150 min/week.³¹ After 72 weeks of treatment, mean WL was 15–20.9% (versus 3.1% with placebo) with 30–57% of participants achieving \geq 20% WL (Table 1).³¹ Physical function improved more with tirzepatide than with placebo and 95% of people with prediabetes reverted to normoglycaemia.³¹

The most commonly reported adverse effects were nausea, diarrhoea and vomiting,¹⁸ most of which were mild to moderate in severity and improved over time. Only 4.3–7.1% of participants in SURMOUNT-1 and 3–11% in the SURPASS programme discontinued the medication because of adverse effects.¹⁸ People with T2DM did not experience a higher risk of hypoglycaemia, except if tirzepatide was combined with sulfonylurea or insulin. In SURMOUNT-1, an increased risk of cholecystitis compared with placebo was observed, possibly because of marked WL, but the overall incidence was $<$ 0.6%.

Tirzepatide also improved multiple cardiometabolic risk factors, such as waist circumference, systolic and diastolic blood pressure and lipid profile, in both SURMOUNT-1 and the SURPASS programme.^{18,31} In people with T2DM, tirzepatide also led to a clinically important reduction in liver fat content and visceral adipose tissue; in addition, in those with T2D and high cardiovascular risk, tirzepatide also delayed the estimated glomerular filtration rate (eGFR) decline and reduced the urine albumin:creatinine ratio compared with insulin glargine.^{32,33}

A prespecified cardiovascular meta-analysis of the SURPASS programme compared the time to first occurrence of a four-point major adverse cardiovascular event (MACE), comprising cardiovascular death, myocardial infarction, stroke and hospitalisation for unstable angina, between the pooled tirzepatide and control groups.³⁴ In a T2DM population, with one-third having established cardiovascular disease and follow-up just over 1 year, there was no evidence of excess cardiovascular risk with tirzepatide versus its comparators (hazard ratio 0.80 (95% CI: 0.57–1.11) for MACE-4 and 0.90 (95% CI: 0.50–1.61) for cardiovascular death).³⁴

Further studies assessing the impact of tirzepatide in different populations with obesity (SURMOUNT-2, NCT04657003) as well as with multiple obesity-related complications, such as non-alcoholic steatohepatitis (NASH, NCT04166773), heart failure with preserved ejection fraction (NCT04847557), obstructive sleep apnoea (NCT05412004) and cardiovascular disease (NCT04255433), are ongoing.

Pharmacotherapies in the pipeline based on gut hormone combinations with GLP1

Dual agonism with amylin

Amylin is a hormone co-secreted with insulin from pancreatic β -cells in response to food intake. It is implicated in satiety regulation through actions in the brain and improves glycaemic control by delaying gastric emptying and inhibiting glucagon secretion.³⁵

Cagrilintide is a long-acting amylin analogue administered once weekly subcutaneously. In a phase II trial, 26 weeks of cagrilintide in doses up to 4.5 mg resulted in greater WL compared with placebo in people with obesity (6.0–10.8% versus 3.0%) and, at the 4.5 mg dose, cagrilintide was superior to liraglutide 3 mg for WL (10.8% versus 9.0%).³⁶ Cagrilintide was well tolerated, with dropouts predominantly resulting from gastrointestinal side effects, which were comparable to those of liraglutide.³⁶

WL through GLP1 RAs and amylin analogues is mediated through both distinct and overlapping pathways; thus, combined therapy could yield synergistic effects with respect to WL by reducing appetite further.³⁵ In a phase Ib study, the combination of cagrilintide 2.4 mg plus semaglutide 2.4 mg once weekly (CagriSema) in people with obesity resulted in 17.1% WL after 20 weeks compared with 9.8% WL with placebo plus semaglutide 2.4 mg, without worsening tolerability.³⁷ A press release of the phase II study results revealed that, in people with T2DM and obesity, 32 weeks of CagriSema resulted in more WL (15.6%) compared with semaglutide 2.4 mg (5.1%) and cagrilintide 2.4 mg (8.1%) alone, as well as superior HbA1c reduction, suggesting a potential synergistic action.³⁸ A phase III programme (REDEFINE, NCT05567796) assessing the safety and efficacy of CagriSema in different populations with obesity is ongoing.

Dual agonism with glucagon

Glucagon is secreted from pancreatic α -cells in response to low blood glucose levels. It increases blood glucose through hepatic glucose production, but also reduces food intake, increases energy expenditure and promotes hepatic fatty acid oxidation.³⁹

Combining glucagon with GLP1 actions could improve WL while protecting against the diabetogenic risk of glucagon agonism. Initial results from studies in animals were encouraging and led to the development of numerous GLP1/glucagon co-agonists. Various levels of efficacy regarding WL have been reported in humans with different GLP1/glucagon co-agonists in early-phase clinical trials (Table 2).

In a phase II trial in people with T2DM and obesity, BI 456906 led to a dose-dependent WL of up to 9.0% at 16 weeks compared with 1.2% with placebo and 5.4% with semaglutide 1 mg.⁴⁰ Moreover, HbA1c reduced more with BI456906 compared with placebo and semaglutide 1 mg (Table 2).⁴¹ Efinopegdutide (JJ-64565111; HM12525A) also led to dose dependent

Table 1. Efficacy of tirzepatide 5, 10 and 15 mg in phase III global clinical trials for type 2 diabetes mellitus and obesity management

Study	No. of participants	Comparator	Indication	Follow-up	Background therapy for T2DM	Baseline BMI (kg/m ²)	Baseline HbA1c (%)	Weight loss versus comparator	≥ 15% WL versus comparator (proportion %)	HbA1c (%) change versus comparator	≤ 6.5% HbA1c versus comparator (proportion %)
SURPASS-1 ^{24,25}	478	Placebo	T2DM	40 weeks	Diet and exercise	31.9	7.94	-6.3 to -7.8 kg versus -1 kg ETD: -5.3 to -6.8 kg	12-23/0	-1.69 to -1.75 versus -0.09 ETD: -1.6 to -1.66	73-75/11
SURPASS-2 ²⁵	1,879	Semaqlutide 1 mg	T2DM	40 weeks	Metformin	34.2	8.29	-7.6 to -11.2 kg versus -5.7 kg ETD: -1.9 to -5.5 kg	15-36/8	-2.01 to -2.3 versus -1.86 ETD: -0.15 to 0.45	69-80/64
SURPASS-3 ^{26,27}	1,444	Insulin degludec	T2DM	52 weeks	Metformin ± SGLT-2i	33.5	8.17	-7 to -11.3 kg versus +1.9 kg ETD: -8.9 to -13.2 kg	12-35/0	-1.85 to -2.14 versus -1.25 ETD: -0.60 to -0.89	67-74/42
SURPASS-4 ²⁷	2,002	Insulin glargine	T2DM	52 weeks	≤ 3 oral glucose-lowering agents	32.6	8.52	-6.4 to -10.6 kg versus +1.7 kg ETD: -8.1 to -12.3 kg	13-33/<1	-2.11 to -2.41 versus -1.39 ETD: -0.72 to -1.02	62-74/31
SURPASS-5 ²⁸	475	Placebo	T2DM	40 weeks	Insulin glargine ± metformin	33.2-33.6	8.31	-5.4 to -8.8 kg versus +1.6 kg ETD: -7.1 to -10.5 kg	7-24/0	-2.11 to -2.4 versus -0.86 ETD: -1.24 to -1.53	74-86/17
SURMOUNT-1 ³¹	2,539	Placebo	Obesity	72 weeks	NA	38.0	5.6	-15% to -20.9% versus -3.1% ETD: -11.9 to -17.8%	48-71/9	NA	NA

ETD = estimated treatment difference; HbA1c = glycosylated haemoglobin; NA = not applicable; SGLT-2i = sodium-glucose co-transporter-2 inhibitors; T2DM = type 2 diabetes mellitus; WL = weight loss.

Table 2. Efficacy in early-phase clinical trials with pharmacotherapies based on combinations of gut hormones

Medication	Mechanism of action	Clinical trial phase	No. of participants	Doses assessed	Follow-up (weeks)	Baseline BMI (kg/m ²)	Baseline HbA1c (%)	Comparator	Weight loss versus comparator	HbA1c (%) change versus comparator
People with obesity (without diabetes)										
Efinopeglutide ⁴³ (INJ-6456511; HM12525A)	GLP1R + GCGR agonist	2	474	5, 7.4, 10 mg qw s/c	26	40.5	5.5	Placebo Liraglutide 3 mg	-8.5 to -11.8% versus -1.8% ETD: -6.7% to -10.0% -8.5 to -11.8% versus -7.5% ETD: -1 to -4.3%	+0.03 to +0.08 versus +0.03 ETD: 0 to +0.05 +0.03 to +0.08 versus -0.24 ETD: +0.27 to +0.32
Pemvidutide (ALT-801) ⁴⁵	GLP1R + GCGR agonist	2	160	1.2, 1.8, 2.4 mg qw s/c	24	36	5.5-5.6	Placebo	-7.3 to -10.7% versus -1% ETD: -6.3 to -9.7%	NR
CagriSema ³⁷	GLP1R + amylin receptor agonist	1b	96	2.4 mg /0.16, 0.3, 0.6, 1.2, 2.4, 4.5 mg ^c qw s/c	20	32.1	5.3	Placebo	-8.3% to -17.1% versus -9.8% ETD: +1.4 to -7.4%	0 to -0.4 versus -0.2
AMG-133 ⁴³	GLP1R agonist + GIPR antagonist	1	75	140, 280, 420 mg q4w s/c	12	33.4-33.5	NR	Placebo	-7.2% to -14.3% versus NR	NR
People with T2DM										
CagriSema ^{b,38}	GLP1R + amylin receptor agonist	2	92	2.4 mg/2.4 mg qw s/c	32	NR	8.4	Semaglutide 2.4 mg qw Amylin 2.4 mg qw	-15.6% versus -5.1% ETD: -10.5% -15.6% versus -8.1% ETD: -7.5%	-2.18 versus -1.79 ETD: -0.39 -2.18 versus -0.93 ETD: -1.25
Efinopeglutide ⁴² (INJ-6456511)	GLP1R + GCGR agonist	2	195	5, 7.4, 10 mg qw s/c	12	40.3	7.6	Placebo	-5.3% to -7.9% versus -0.7% ETD: -4.6 to -7.2%	0.0 to -0.1 versus -0.1 ETD: +0.1

Table 2. Efficacy in early-phase clinical trials with pharmacotherapies based on combinations of gut hormones (Continued)

Medication	Mechanism of action	Clinical trial phase	No. of participants	Doses assessed	Follow-up (weeks)	Baseline BMI (kg/m ²)	Baseline HbA1c (%)	Comparator	Weight loss versus comparator	HbA1c (%) change versus comparator
BI 456906 ^{64,60}	GLP1R + GCGR agonist	2	411	0.3, 0.9, 1.8, 2.7 mg qw and 1.2, 1.8 mg biw s/c	16	34	8.1	Placebo Semaglutide 1 mg qw	-1.9% to -9.0% versus -1.2% ETD: -0.7 to -7.8% -1.9% to -9.0% versus -5.4% ETD: +3.5 to -3.6%	-0.93 to -1.88 versus -0.25 ETD: -0.68 to -1.63 -0.93 to -1.88 versus -1.47 ETD: +0.54 to -0.41
Cotadutide ⁴⁴ (MEDI0382)	GLP1R + GCGR agonist	IIb	834	100, 200, 300 mcg qd s/c	54	34.2–35.4	8.1–8.2	Placebo Liraglutide 1.8 mg qd	-3.2% to -5.0% versus -0.7% ETD: -2.5 to -4.3% -3.2% to -5.0% versus -3.3% ETD: +0.1 to -1.7%	-1.03 to -1.19 versus -0.45 ETD: -0.58 to -0.74 -1.03 to -1.19 versus -1.17 ETD: +0.14 to -0.02
SAR425899 ⁶⁵	GLP1R + GCGR agonist (substudy)	IIb	70	0.12, 0.16, 0.20 mg qd s/c	26	32.1–34.8	8.0–8.3	Placebo Liraglutide 1.8 mg qd	-4 versus -1% ETD: -3% -4 versus -5% ETD: 1%	-1.9 versus -1.2 ETD: -0.7 -1.9 versus -1.4 ETD: -0.5
Retatrutide ⁴⁸ (LY3437943)	GLP1R + GIPR + GCGR agonists	Ib	72	0.5, 1.5, 3, 3/6, 3/6/9/12 mg qw s/c	16	32.1	8.7	Placebo Dulaglutide 1.5 mg qw	-2.1 to -8.6 kg versus +0.3 kg ETD: -2.4 kg to -9 kg -2.1 to -8.6 kg versus +0.4 kg ETD: -2.5 to -9 kg	-1.18 to -1.90 versus -0.34 ETD: -0.84 to -1.56 -1.18 to -1.90 versus -0.96 ETD: -0.22 to -0.94

biw = twice weekly; BMI = body mass index; ETD = estimated treatment difference; GCGR = glucagon receptor; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP1R = glucagon-like peptide 1 receptor; HbA1c = glycosylated haemoglobin; NR = not reported; q4w = once every 4 weeks; qd = once daily; qw = once weekly; s/c = subcutaneous; T2DM = type 2 diabetes mellitus. ⁶⁰Abstract presentation. ⁶⁵Company press release. ^{62,64}mg corresponds to semaglutide 2.4 mg and the escalated doses 0.16 to 4.5 mg correspond to the amylin analogue cagrilintide. For the category of dual GLP1/glucagon agonists, we have included in this table only those that have phase II clinical trial data.

placebo-adjusted WL of up to 7.2% after 12 weeks of treatment in a phase II trial in people with obesity and T2DM; however, HbA1c did not improve.⁴² In people with obesity (without diabetes), the highest dose of efinopegdutide led to a placebo-adjusted WL of 10% after 26 weeks.⁴³

Cotadutide 300 mg was superior for WL (5.02%) compared with placebo (0.68%) and liraglutide 1.8 mg (3.33%) in a 54-week phase IIb trial in people with T2DM and obesity, and reduced HbA1c to similar levels to those achieved with liraglutide 1.8 mg.⁴⁴ The improvements seen in hepatic parameters with cotadutide led to a phase III trial assessing its safety and efficacy for NASH and fibrosis (NCT05364931). In a phase II study, pemvidutide (ALT-801) resulted in dose-dependent placebo-adjusted WL of up to 9.7% after 24 weeks in people with obesity, and is also being assessed as a treatment for NASH.⁴⁵

The most commonly reported adverse effects with dual GLP1/glucagon agonists were gastrointestinal (nausea and vomiting).

Triple agonism (GLP1/GIP/glucagon)

Given the efficacy and benefits of the dual GLP1/GIP receptor agonist tirzepatide and the dual GLP1/glucagon receptor agonists, a triple agonist targeting all three receptors (GLP1/GIP/glucagon) could result in superior WL and glycaemic control compared with dual agonists.⁴⁶ LY3437943 (retatrutide), a new triple agonist, resulted in more WL compared with tirzepatide in preclinical studies and also improved the glucose profile.⁴⁷ In a phase Ib trial in people with T2DM, retatrutide once weekly subcutaneously for 12 weeks led to a placebo-adjusted HbA1c reduction of up to 1.6% and dose dependent placebo-adjusted WL of up to 8.96 kg in the highest dose group.⁴⁸ The safety profile of LY3437943 was comparable to that of other incretin medication.⁴⁸ A phase II trial was recently completed (NCT04881760) and a phase III programme will start later in 2023.

GIP antagonists in combination with GLP1 RAs

Not only the agonism of the GIP receptor results in WL; interestingly, antagonism of the GIP receptor could also be a potential obesity treatment. Antagonism of this receptor was shown in preclinical studies to improve the metabolic profile and reduce food intake.^{49,50} The molecular mechanisms explaining the similar effect of GIP receptor agonists and antagonists are under investigation.⁵¹ These effects are further amplified by combining a GIP receptor antagonist with a GLP1 receptor agonist.⁵² Thus, AMG-133, a once-monthly subcutaneous injection, was designed and, in a phase I study, resulted in mean WL between 7.2% and 14.5% after 12 weeks in people with obesity (without diabetes).⁵³ The main side effects were nausea and vomiting, which subsided after 48 h. A phase II trial is ongoing (NCT05669599).

Other pharmacotherapies in the pipeline not based on gut hormones

Despite the main research focus for future obesity treatments being on gut hormone combinations, treatments targeting different pathways are also under investigation. Bimagrumab, an intravenous four-weekly human monoclonal antibody against the activin type II receptor, promotes skeletal muscle growth and reduces fat mass, suggesting it as a treatment for sarcopenic obesity.⁵⁴ In a phase II trial, 48 weeks of bimagrumab in people

with T2DM and obesity led to 6.5% WL (5.9 kg) versus 0.5% WL with placebo, and a subsequent reduction in total body fat mass of 7.49 kg with a small increase in lean mass. HbA1c improved by 0.76% with bimagrumab, but remained stable with placebo.⁵⁴ A phase II trial assessing the safety and efficacy of bimagrumab in combination with different doses of semaglutide in people with obesity is ongoing (NCT05616013).

A new era in obesity management and considerations for novel and future pharmacotherapies

Tirzepatide marks a new era in obesity pharmacotherapy in which a combination of gut hormones can approach the WL achieved with bariatric surgery. Several novel, gut hormone-based, dual and triple agonists are undergoing phase III clinical trials as potential obesity and T2D treatments. However, many clinical considerations need to be addressed over the next few years so that novel and future obesity pharmacotherapies become more widely accepted by healthcare systems, healthcare professionals and people living with obesity.

GLP1 RAs in doses approved for T2DM management have shown cardioprotective effects in people with T2DM and established cardiovascular disease.^{9,49,50,52} Nevertheless, whether the combination of GLP1 RAs with other gut hormones will improve cardiovascular outcomes in people with T2DM needs to be established. The SURPASS-CVOT trial (NCT04255433) will assess the cardiovascular safety of tirzepatide compared with dulaglutide, a GLP1 RA with established cardiovascular benefits, in people with T2DM and established atherosclerotic disease. Currently, the updated American Diabetes Association (ADA)/European Association for the study of Diabetes (EASD) consensus guidelines for management of hyperglycaemia in T2DM recommend tirzepatide as treatment with very high efficacy in achieving glycaemic and WL targets; however, for people with T2DM and established cardiovascular disease or very high cardiovascular risk, GLP1 RAs with proven cardiovascular benefits and/or sodium-glucose co-transporter-2 inhibitors remain the recommended glucose-lowering treatments.

No pharmacological treatment for obesity has yet shown a reduction in major cardiovascular events in people without diabetes. The SELECT trial (NCT03574597) is investigating the effect of semaglutide 2.4 mg in major adverse cardiovascular events in people with obesity and established cardiovascular disease (completion date September 2023), whereas the SURMOUNT-MMO (tirzepatide, NCT05556512) is assessing the impact of combined gut hormone therapies in cardiovascular outcomes and all-cause mortality for people with obesity (without diabetes).⁹

Similar to other chronic diseases, such as hypertension, obesity requires long-term treatment; if obesity medications are effective and well tolerated, then the treatment should be continued, otherwise the disease will relapse and weight regain will occur in most patients, as demonstrated in the STEP-1 extension trial with semaglutide 2.4 mg.^{55,56} However, the data on long-term clinical effectiveness and safety for the new obesity treatments are limited and further studies are needed to inform the optimal treatment regimens for long-term use. Moreover, because the new treatments for obesity approach the efficacy of bariatric surgery regarding WL, it remains to be elucidated whether they will be also associated with long-term complications similar to bariatric surgery, such as increased risk of micronutrient deficiencies, substantial muscle mass loss, psychological complications and fractures.^{57,58}

The concept of combining different treatment modalities with complementary actions is standard of care for several complex and chronic diseases.⁵⁹ In obesity management, it is becoming increasingly evident that we also need to focus on a multimodal approach (combining lifestyle interventions, pharmacotherapy, endoscopic procedures and bariatric surgery) to achieve over time the personalised WL and metabolic targets required for health gain, because, even after bariatric surgery, weight regain is common and leads to recurrence of obesity-related complications.^{60,61} Combination treatments should not be offered as a last resort, but instead even as a first line for people with severe and complex obesity. Thus, the traditional stepwise approach to obesity management should be challenged and therapies adjusted to the individual. The efficacy and safety of novel and future obesity pharmacotherapies in combination with other treatment modalities (eg intensive lifestyle interventions or bariatric surgery) requires further investigation. Nevertheless, data from clinical trials with GLP1 RAs suggest that gut hormone-based treatments remain effective in improving glycaemic control and WL in people who have undergone bariatric surgery and experience inadequate WL and/or control of obesity-related complications.^{62,63}

Ensuring equal access to the novel pharmacotherapies through their approval from private and public payers could become challenging because of their cost; long-term data on the clinical effectiveness of new obesity pharmacotherapies will support the robustness of cost-effectiveness analyses. Pragmatic prescribing pathways targeting long-term use of novel pharmacotherapies to populations who will likely benefit most from their use (eg people with severe and complex obesity who achieve specific WL targets with pharmacotherapy at prespecified time points) could further optimise the health economics and improve access to these treatments.⁶⁴ Additionally, with so many molecules competing for a place on the market and with older molecules losing their patent, medications might become less expensive, further boosting their cost-effectiveness.

Conclusion

Tirzepatide, the first approved dual agonist (GLP1 and GIP receptors) for T2DM management, also marks a new era for obesity pharmacotherapies, where mean WL approaches that of bariatric surgery. Multiple other gut hormone combinations are under investigation as potential future therapies for obesity and metabolic complications. Between them, CagriSema and the triple agonist retatrutide are the furthest advanced in clinical development and have progressed to phase III trials. Additional research assessing the long-term safety, clinical effectiveness and cost-effectiveness of new and future obesity pharmacotherapies will help us understand better their position in treatment algorithms for WL and obesity-related complications, as part of an integrated multimodal approach aiming to support people with obesity achieving and maintaining individualised WL and metabolic targets. ■

Declaration of interests

EM declares no conflict of interest. ADM has received grants or contracts from Fractyl, Novo Nordisk and Randox, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novo Nordisk, AstraZeneca,

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Key points

- > A better understanding of the role of gut hormones in the regulation of appetite and glucose homeostasis has led to the discovery of glucagon-like peptide 1 (GLP1) receptor analogues (RAs), which are established treatments for obesity and type 2 diabetes mellitus (T2DM).
- > In the search for the next generation of obesity pharmacotherapies, multiple combinations of GLP1 receptor agonists with other gut hormones (amylin, glucose-dependent insulinotropic polypeptide (GIP) and glucagon) with diverse metabolic actions are under development as dual or triple agonists.
- > Tirzepatide 5–15 mg is the first dual GLP1 and GIP receptor agonist approved for T2DM management and, in people with obesity without diabetes, resulted in up to a 20.9% weight loss with good tolerability (phase III trial data).
- > The combination of the amylin analogue cagrilintide with the GLP1 RA semaglutide 2.4 mg (CagriSema) as well as the triple agonist (GLP1/GIP/glucagon) retatrutide could bridge further the efficacy gap between bariatric surgery and pharmacotherapies; both drugs have progressed to phase III trials.
- > Oral GLP1 receptor analogues (oral semaglutide and danuglipron) are also under investigation as potential obesity treatments.
- > The long-term safety, clinical effectiveness and cost-effectiveness of novel and future pharmacotherapies for obesity and T2DM require further evaluation to help us understand better their position in treatment algorithms.

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Address for correspondence: Dr Dimitris Papamargaritis, Diabetes Research Centre, Leicester General Hospital, Leicester, LE5 4PW, UK.
Email: dp421@leicester.ac.uk