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REVIEW

Polyagonists in Type 2 Diabetes Management

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Abstract

Purpose of the Review This review summarizes the new developments in polyagonist pharmacotherapy for type 2 diabetes.
Recent Findings Several dual- and triple-agonists targeting different pathogenic pathways of type 2 diabetes have entered clinical trials and have led to significant improvements in glycaemia, body weight, fatty liver, and cardio-renal risk factors, with variable adverse event profiles but no new serious safety concerns. Combining agents with complementary and synergistic mechanisms of action have enhanced efficacy and safety. Targeting multiple pathogenic pathways simultaneously has led to enhanced benefits which potentially match those of bariatric surgery. Tirzepatide, cotadutide, BI456906, ritatrutide, and CagriSema have entered phase 3 clinical trials. Outcomes from published clinical studies are reviewed. Efficacy-safety profiles are heterogeneous between agents, suggesting the potential application of precision medicine and need for personalized approach in pharmacological management of type 2 diabetes and obesity.
Summary Polyagonism has become a key strategy to address the complex pathogenesis of type 2 diabetes and co-morbidities and increasing number of agents are moving through clinical trials. Heterogeneity in efficacy-safety profiles calls for application of precision medicine and need for judicious personalization of care.

Keywords Type 2 diabetes · Dual agonist · Triagonist · Polyagonist · Twincretin

Introduction

Diabetes mellitus affects 537 million adults around the world and is expected to rise to 783 million by 2045 [1]. Nearly 90% of these individuals have type 2 diabetes (T2D). Diabetes is the ninth leading cause of deaths around the world and a major risk factor for the top two leading causes of death—ischaemic heart disease and stroke [2]. Diabetes management is multi-target oriented: improving glycaemia, preventing cardiovascular and renal disease, improving quality of life and survival, managing co-morbidities, and minimizing treatment burden.

Multiple hormones regulate glucose and energy homeostasis, and these have become new targets for pharmacological manipulation. Review of their physiological and pathophysiological effects is beyond the scope of this paper and has been described in recent in-depth reviews [3–7, 8••] (see Fig. 1 for a summary). Discovery of incretin effect, identification of glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) as incretin hormones and isolating exendin-4 from Gila monster venom as structurally homologous to GLP-1 culminated in developing exendin-4 analogues (exenatide, lixisenatide) followed by GLP-1 receptor agonists (GLP-1-RAs) (liraglutide, dulaglutide, semaglutide) adding to the therapeutic repertoire [8••]. Added advantages of weight reduction, improving cardiovascular and renal outcomes [9], extending the half-life of molecules to enable weekly administration [10], developing oral preparations (oral semaglutide), and more recently, development of a non-peptide small molecule GLP-1RA (orforglipron) [11] have made modulation of hormone targets a key strategy in management of T2D and its co-morbidities like obesity and fatty liver disease.

However, the benefits of GLP-1RAs did not reach the magnitude of that seen with bariatric surgery. Gastrointestinal adverse effects were a limiting factor at least for some [12]. Most other peptide hormones in isolation did not deliver meaningful benefits. The success of bariatric surgery

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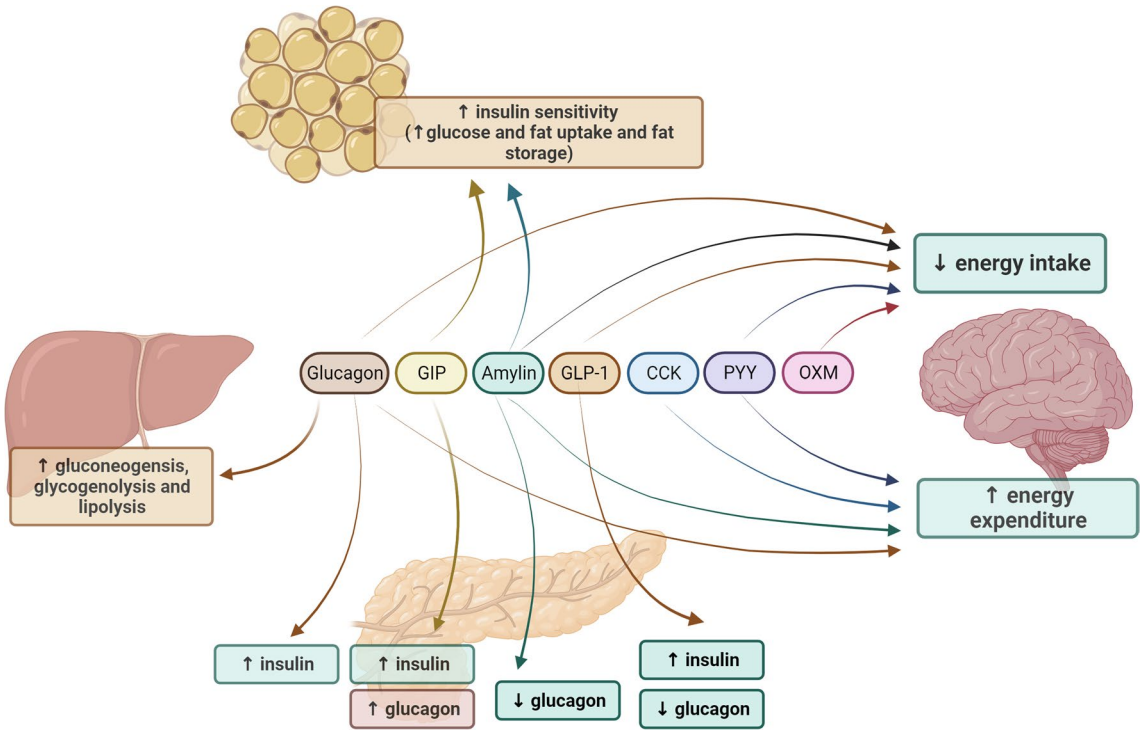

Fig. 1 Role of key hormones in glucose and energy homeostasis. Glucagon, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and oxyntomodulin (OXM) are preproglucagon derivatives with varying effects on the pancreas, liver, adipose tissue, and brain to regulate glucose and energy homeostasis. Cholecystokinin (CCK) and peptide-tyrosine-tyrosine (PYY) are pancreatic peptides predominantly act through central mechanisms to regular energy intake and expenditure (image created using BioRender.com)

in reducing weight, improving glycaemia, and even achieving remission of T2D is attributed to changes in multiple hormones in gut-brain-pancreas cross talk, hence the value of unimolecular polypharmacy, i.e., single molecules that target more than one receptor.

In this review, we highlight the recent developments in unimolecular polyagonists in the treatment of T2D, highlight data from clinical trials and explore the potential for precision medicine in T2D care with different polyagonists.

Unimolecular Polypharmacy

Rationale

Co-morbidities and complications of T2D require treatment targeting multiple pathogenic mechanisms. Single agent is unlikely to address all pathways involved. Polypharmacy with multiple agents is unlikely to be acceptable, affordable, or safe, hence the value of medications with multiple targets. Co-administration of peptides are challenging due to discrepancies in their pharmacokinetics and due to peptide—peptide interactions [13]. Developing a single peptide molecule with ability to act on more than one target receptor is an attractive alternative [14].

Harnessing the complementary and synergistic effects of polyagonism is another advantage of unimolecular polypharmacy. For example, GIP agonists as monotherapy was not effective in treating T2D: it increased glucagon, had less insulinotropic effect in people with diabetes, did not reduce appetite, increased adiposity, and did not decrease glucose level in people with T2D [15]. It was not expected to work well in combination with a GLP-1 agonist either, as it antagonized appetite suppressant effects of GLP-1RA in human studies, had no additive increase in insulin release, and blunted the glucagonostatic effects of GLP-1 agonists [16, 17]. However, all drawbacks of GIP were based on short term infusions of GIP and long-lasting GIPs were not available for study in humans [8••]. GIP's weak insulinootropic effects in people with T2D is largely due to post-receptor signalling defects in beta cells [18] and to some extent, due to hyperglycaemia-induced suppression of GIP receptor expression in beta cells [19]. Reducing the level of glycaemia (with GLP-1 for example) could therefore make the beta cells more responsive to GIP. GIP could potentiate the effects of GLP-1 by accelerating the recycling of GLP-1-receptors [20]. The undesirable effects of GIP mediated

glucagonotropism on raising blood glucose could potentially be overcome by the overall glucose lowering effect of GLP-1, thus making the two targets complementary to each other [21].

The first GLP-1/GIP dual agonist was not superior to liraglutide [22], but tirzepatide was superior to the active comparator dulaglutide 1.5 mg once a week [23]. Subtle changes in the GLP-1 and GIP molecules alter the post-receptor signalling pathways activated (i.e., biased agonism) in such a way that the receptor down regulation is minimally affected. The overwhelming success of tirzepatide may at least partly be due to such a structural uniqueness that leads to decreased receptor down regulation at one or both receptors [21]. Finally, the centrally mediated anti-emetic effects of GIP may mitigate the centrally mediated adverse effects of GLP-1 like nausea/vomiting thus making the combination more tolerable [24]. For an example adverse events of tirzepatide 10 mg once a week injection was not worse than dulaglutide 1.5 mg once a week, but the former conferred greater weight loss and HbA1c improvement [25].

Similarly, the combination of GLP-1 and glucagon agonists, when made in correct proportions can harness the weight loss effects of both receptor activities and utilize the liver-friendly actions of glucagon while using the glucose lowering effects of GLP-1 to overcome the potential hyperglycaemic effects of glucagon. Likewise, combination of all the pre-proglucagon derived peptides could yield synergistic benefits: potent insulinotropism of GLP-1 and GIP overcoming glucagon-mediated hyperlgycaemia and potent weight reducing effects of GLP-1 and glucagon overcoming the appetite stimulating and adipocyte expanding effects of GIP.

Development of Polyagonists

Structural similarities of pre-proglucagon derivatives make them candidates for unimolecular polyagonists [26]. Native glucagon peptide sequence was modified to develop of GLP-1/GCGR [27] and GLP-1/GIP [28] dual agonists. Similarly, modification of glucagon molecule to increase its affinity to GIP and GLP-1 receptors (YAG glucagon [14], HM15211 [29]); fusion of GIP and oxyntomodulin peptide segments ([DA2]GIP-Oxm [30]); fusion of key amino acid sequences from GIP, GLP-1, and glucagon ([DA2]GLP-1/GCG [31]); and addition on GCGR agonistic amino acid sequence to previously developed GIP/GLP-1 dual agonist [32] are some of the strategies used to develop triagonists.

In contrast, peptides with fundamentally different structures can be combined using recombinant gene technology to produce a recombinant fusion protein. Examples are AC164204 and AC164209, which are hybrids of amylin analogue davalintide and GLP-1 analogue exenatide [33], C218 (CCKR1 agonist and GLP-1RA hybrid peptide peptide) and CCK-4/exendin-4 hybrid peptide. Antibody–drug combinations are increasingly used to develop molecules acting on multiple target receptors (e.g., maridebart-cafraglutide [AMG133]—an IgG immunoglobulin with GIPR antagonism bound to two GLP-1 analogues).

Several polyagonists in development are summarized in Table 1.

Clinical Outcomes

Efficacy

GLP-1/GIP Dual Agonists

Tirzepatide is a GLP-1/GIP dual agonist approved by FDA for the treatment of T2D. It has shown greater reduction in HbA1c and weight than any other single pharmacological agent. A network meta-analysis comparing ten incretin-based therapies, as add-ons to metformin showed tirzepatide 15 mg once a week to have the highest reduction in HbA1c (−2.23 [95% CI −2.45, −2.01]%) and weight (11.33

Table 1 Polyagonists in clinical trials

Agent	Mechanism of action	Route and frequency of administration	Active trials	Phase
Tirzepatide (LY3298176)	GLP-1/GIP dual agonists	Subcutaneous once a week	Multiple (see text)	3
CT-868	GLP-1/GIP dual agonists	Subcutaneous once a day	NCT05110846	2
VK2735/VK2735-oral	GLP-1/GIP dual agonists	Subcutaneous once a week/oral once daily	NCT05203237	1
LY-3537031	GLP-1/GIP dual agonists	Subcutaneous	NCT04648865	1
CT-388	GLP-1/GIP dual agonists	Subcutaneous once a week	NCT04838405	1
DR10627, DR10628	GLP-1/GIP dual agonists	Subcutaneous	CTR20232870	1
BI456906	GLP-1/GCGR dual agonist	Subcutaneous once or twice a week	NCT06066528	3
HEC88473	GLP-1/FGF21 dual agonist	Subcutaneous once a week	NCT05943886	1
Maridebart cafraglutide (AMG133)	GLP-1R agonist/GIPR antagonist	Subcutaneous injection once in 4 weeks	NCT05669599	2
Retatrutide (LY3437943)	GLP-1, GIP, GCGR triagonist	Subcutaneous once a week	NCT05929079	3
DR10624	GLP-1, GCGR, FGFR21 triagonist	Subcutaneous injection	NCT05378893	1

[95% CI − 13.15, − 9.52] kg) while the next best reductions were with semaglutide 1 mg once weekly (HbA1c change by − 1.57 [95% CI − 1.81, − 1.33]%) and weight change by − 5.99 [95% CI − 7.78, − 4.19] kg) compared to placebo [34] (Table 2). Similarly, compared to basal insulin, tirzepatide yields greater reduction in HbA1c (HbA1c − 0.90 [95% CI − 1.06, − 0.75]%) and weight (95% CI − 12.0 [− 13.8, − 10.1] kg, for pooled doses) [35].

A pre-specified meta-analysis of data from randomized controlled trials (RCTs) on 4-point major adverse cardiovascular events (MACE) (time to first event analysis) reported there was no increase in events among individuals treated with tirzepatide. All studies were of short term and not designed to evaluate cardiovascular safety or efficacy [36•]. Furthermore, tirzepatide improved cardiovascular risk factors [37], biomarkers (YKL-40, hsCRP, and ICAM-1 and leptin) [38], and atherogenic lipids (triglyceride-rich lipid particles, small-LDL particles, apoCIII, and apoB) [39]. Furthermore, significant blood pressure reduction (SBP/DBP 2.8–12.6/0.8–4.5 mmHg) were observed in SURPASS trials [40••, 41–44]. SURPASS-CVOT (NCTLY3298176) is currently in progress, evaluating the hard cardiovascular endpoints with tirzepatide treatment in people with T2D against an active comparator (dulaglutide) and will be completed in 2024.

Tirzepatide may improve kidney and liver-related outcomes as well as quality of life [45]. Meta-analysis of published RCTs have suggested that tirzepatide significantly improves kidney specific outcomes (HR 0.55, 95% CI 0.40–0.77) and worsening of albuminuria (HR 0.38, 95% CI 0.24–0.61) with a margin greater than other GLP-1RAs overall (HR 0.79 [95% CI 0.75–0.85] for kidney specific outcomes and HR 0.76 [95% CI 0.71–0.82] for progression of albuminuria). However, renal outcomes were not the primary endpoints in included studies [46]. A decrease in liver enzymes was demonstrated across phase 3 trials (reduced aspartate aminotransferase (AST) by 29–216% and alanine transaminase (ALT) by 222–232%) [43, 44, 47, 48]. SURPASS-3 MRI, a sub-study of the SURPASS-3 trial, reported significant reductions in liver fat content (absolute reduction in liver fat content − 8·09% [SE 0·57] with tirzepatide 10 or 15 mg per week Vs − 3·38% [SE 0·83] with insulin degludec, estimated treatment difference − 4·71% [95% CI − 6·72 to − 2·70; $p < 0·0001$]) in participants with elevated liver fat content at baseline [47]. The potential role of tirzepatide in non-alcoholic steatohepatitis (NASH) will be further evaluated in the phase 2 SYNERGY-NASH trial (NCT04166773), a 52-week RCT among people with NASH with fibrosis with or without diabetes comparing weekly tirzepatide 5, 10, and 15 mg against placebo.

Series of other phase 3 trials are underway evaluating the role of tirzepatide at different stages of diabetes treatment (monotherapy as first line, add-on to metformin, add-on at oral treatment failure, switching from a GLP-1 receptor agonist [NCT05536804, NCT05706506], high dose therapy for adults withT2D, and obesity [NCT06037252]), as well as for specific outcomes (NASH [NCT05751720], HFpEF in people with obesity [NCT04847557], CKD [NCT05536804], coronary artery disease progression [NCT03482024]) and in specific populations (CKD [NCT03482024], lactating females [NCT05978713], and children [NCT05260021]).

GLP-1/GCGR Dual Agonists

Cotadutide is a linear chimeric peptide with GLP-1/glucagon receptor dual agonism, administered daily as a subcutaneous injection. A meta-analysis of nine RCTs concluded that among people with T2D, cotadutide achieved greater reductions in HbA1c (− 0.68 [− 0.58, − 0.79]%) and weight (− 3.31 [− 2.76, − 3.85]%) than placebo [49]. In a phase 2b RCT among adults with body mass index BMI ≥ 25 mg/m^2 and T2D inadequately controlled with metformin, at 54-week follow-up, compared to liraglutide 1.8 mg/day, cotadutide 300 mcg/day achieved similar HBA1c reduction (cotadutide, − 1.19 [− 1.34, − 1.05]% vs. liraglutide, − 1.17 [− 1.38, − 0.98]%; $p = 0.871$) and greater weight reduction (cotadutide, − 5.02 [− 5,78, − 4.26]% vs. liraglutide, − 3.33 [− 4.25, − 2.21]%; $p = 0.009$) from baseline [50•]. Significant improvements in fatty liver-related parameters (AST, ALT, FIB-4 index, NFS score, and Pro-C3 level) were seen with cotadutide 300 mcg/day compared to placebo. The improvements were not statistically significantly superior to liraglutide. Notably, semaglutide achieves greater reductions in HbA1c, weight, and fatty liver parameters compared to liraglutide [51]. Furthermore, liraglutide is licenced to be used in a higher dose (3 mg a day) for treatment of obesity. Cotadutide has not been compared head-to-head against semaglutide or high dose liraglutide in a clinical trial. Phase 2b/3 study on cotadutide for the treatment of non-cirrhotic NASH with fibrosis (PROXYMO-ADV; NCT05364931) is still in progress. It is uncertain if cotadutide would progress to phase 3 trials for treatment of T2D.

SAR425899 is another GLP-1/GCGR dual agonist which progressed into a phase 2 trial. Among adults with T2D and overweight/obesity (BMI 25–45 kg/m^2) on lifestyle modification with or without metformin, treatment with daily subcutaneous injection of SAR425899 at 0.12 mg, 0.16 mg, and 0.20 mg daily for 26 weeks achieved superior HbA1c reduction (− 1.52 [SE 0.14]%, − 1.62 [SE 0.13]%, − 1.56 [SE 0.13]%, respectively), compared to placebo (− 0.66 [SE 0.17]%), and greater weight reduction (− 4.28 [SE 0.56] kg, − 5.33 [SE 0.55] kg, − 4.41 [0.56] kg, respectively) compared to placebo (− 1.76 [SE 0.73] kg) [52]. In the same study, individuals randomized to liraglutide 1.8 mg a day achieved HbA1c reduction of − 1.31 [SE 0.12]% and weight reduction of − 4.59 [SE 0.52] kg (comparison with

Table 2 Summary of efficacy and safety outcomes in clinical trials using polyagonists in the treatment of type 2 diabetes

Agent	Trial phase	Population	Follow-up	Groups	HbA1c drop (percentage points)	% achieving HbA1c < 7%	Weight reduction (from baseline)	% achieving weight loss of			Adverse events (AE) (% of participants, unless otherwise specified)									
								> 5%	> 10%	> 15%	Nausea	Vomiting	Diarrhea	GI adverse events	Pancreatitis	Cholecystitis	Heart rate increase, bpm	Injection site reactions	Serious AE	Treatment discontinuation
Tirzepatide SURPASS-2 (Frias JP et al. 2021)	3	Adults, T2D, HbA1c 7.0–10.5%, BMI ≥ 25 kg/m^2, on metformin	40 weeks	Tirzepatide 5 mg/week SC (n = 470)	− 2.09 (SE 0.047)	85.5	− 7.8 kg (SE 0.33)	68.6	35.8	15.2	17.4	5.7	13.2	40.0	0.0	0.2	2.3	1.9	7.0	6.0
				Tirzepatide 10 mg/week SC (n = 469)	− 2.37 (SE 0.048)	88.9	− 10.3 kg (SE 0.34)	82.4	52.9	27.7	19.2	8.5	16.4	46.1	0.4	0.4	2.2	2.8	5.3	8.5
				Tirzepatide 15 mg/week SC (n = 470)	− 2.46 (SE 0.048)	92.2	− 12.4 kg (SE 0.34)	86.2	64.9	39.9	22.1	9.8	13.8	44.9	0.4	0.4	2.6	4.5	5.7	8.5
				Semaglutide 1 mg/week SC (n = 469)	− 1.86 (SE 0.048)	81.1	− 6.2 kg (SE 0.33)	58.4	25.3	8.7	17.9	8.3	11.5	41.2	0.6	0.0	2.5	0.2	2.8	4.1
Cotadutide (Nahra R et al. 2021)	2b	Adults, T2D, HbA1c 7.0–10.5%, BMI ≥ 25 kg/m^2, on metformin	54 weeks	Cotadutide 100 mcg/day SC (n = 100)	− 1.03 (95% CI 1.25, 0.80)	57.3	− 3.70% (95% CI − 4.91, − 2.50)	40.0	10.7	NR	23.0	10.0	13.0	41.0	NR	NR	3.1 (1.4, 4.8)	16.0	1.0	13.0
				Cotadutide 200 mcg/day SC (n = 256)	− 1.16 (95% CI − 1.29, − 1.02)	54.5	− 3.22% (95% CI − 3.96, − 2.48)	29.6	9.0	NR	33.2	19.9	19.1	58.2	NR	NR	2.6 (1.5, 3.6)	17.2	0.4	15.2
				Cotadutide 300 mcg/day SC (n = 256)	− 1.19 (95% CI − 1.34, − 1.05)	57.8	− 5.02% (95% CI − 5.78, − 4.26)	46.5	15.5	NR	41.0	16.8	10.9	59.4	NR	NR	3.1 (2.0, 4.1)	19.5	0.0	21.5
				Liraglutide 1.8 mg/day SC (n = 110)	− 1.17 (95% CI − 1.37, − 0.98)	61.5	− 3.33% (95% CI − 4.35, − 2.31)	30.8	5.8	NR	15.5	2.7	3.6	27.3	NR	NR	1.9 (0.3, 3.5)	3.6	0.0	1.8
				Placebo SC (n = 112)	− 0.45 (95% CI − 0.65, − 0.24)	24.2	− 0.68% (95% CI − 1.77, 0.42)	9.9	1.1	NR	10.7	4.5	8.9	27.7	NR	NR	− 0.1 (− 1.7, 1.5)	7.1	0.9	4.5
Retatrutide[1,3,4,5] (Rosenstock L et al., 2023)	2	Adults, T2D, HbA1c 7.0–10.5%, BMI ≥ 25 kg/m^2, with or without metformin	36 weeks	Retatrutide 4 mg/week SC (n = 22)	− 1.30 (SE 0.20)	61.0	− 7.92% (SE 1.28)	61.0	22.0	10.0	9.0	4.0	9.0	NR	0.0	0.0	NR[1,3,4,5]	4.0	4.0	0.0
				Retatrutide 8 mg/week SC (n = 25)	− 2.13 (SE 0.17)	82.0	− 16.81% (SE 1.59)	91.0	71.0	57.0	27.0	8.0	19.0	NR	0.0	2.0[2]	NR	4.0	8.0	12.0
				Retatrutide 16 mg/week SC (n = 43)	− 2.16 (SE 0.13)	80.0	− 16.94% (SE 1.30)	94.0	71.0	58.0	20.0	11.0	15.0	NR	4.0	0.0	NR	2.0	4.0	15.0
				Dulaglutide 1.5 mg/week SC (n = 46)	− 1.36 (SE 0.13)	60.0	− 2.02% (SE 0.72)	17.0	2.0	0.0	17.0	9.0	9.0	NR	0.0	0.0	NR	2.0	2.0	2.0
				Placebo SC (n = 45)	− 0.30 (SE 0.24)	22.0	− 3.00% (SE 0.86)	25.0	2.0	2.0	4.0	2.0	4.0	NR	0.0	0.0	NR	4.0	7.0	4.0

Table 2 (continued)

Agent	Trial phase	Population	Follow-up	Groups	HbA1c drop (percentage points)	% achieving HbA1c < 7%	Weight reduction (from baseline)	% achieving weight loss of			Adverse events (AE) (% of participants, unless otherwise specified)									
								> 5%	> 10%	> 15%	Nausea	Vomiting	Diarrhea	GI adverse events	Pancreatitis	Cholecystitis	Heart rate increase, bpm	Injection site reactions	Serious AE	Treatment discontinuation
SAR425899 (NCT02973321)	2	Adults, T2D, HbA1c 7.0–10.0%, BMI 25–45 kg/m^2, on metformin	26 weeks	SAR425899 0.12 mg/week SC (n = 66)	− 1.52 (SE 0.14)	66.7	− 4.3 kg (SE 0.6)	33.3	12.1	NR	45.8	29.2	20.8	NR	0.0	0.0 [1,3,4,5]	NR	1.4	4.2	0.0
				SAR425899 0.16 mg/week SC (n = 66)	− 1.62 (SE 0.13)	68.2	− 5.3 kg (SE 0.5)	45.5	13.6	NR	55.9	23.7	18.6	NR	0.0	0.0	NR	0.0	1.7	0*
				SAR425899 0.20 mg/week SC (n = 64)	− 1.56 (SE 0.13)	65.6	− 4.4 kg (SE 0.6)	35.9	15.6	NR	55.3	36.2	19.2	NR	0.0	0.0	NR	0.0	4.3	0.0
				Liraglutide 1.8 mg/day SC (n = 67)	− 1.31 (SE 0.12)	67.2	− 4.6 kg (0.5)	40.3	9.0	NR	31.3	1.5	12.0	NR	0.0	0.0	NR	1.5	3.0	0.0
				Placebo (n = 33)	− 0.66 (SE 0.17)	36.4	− 1.8 kg (SE 0.7)	3.0	0.0	NR	15.2	6.1	6.1	NR	0.0	0.0	NR	0.0	0.0	0.0
CagriSema (2.4 mg/2.4 mg QW) (Frias JP et al., 2023)	2	Adults, T2D, HbA1c 7.5–10.0%, BMI ≥ 27 kg/m^2, on metformin with or without SGLT2i	32 weeks	CagriSema 2.4/2.4 mg/week (n = 31)	− 2.2 (SE 0.15)	NR	− 15.6% (SE 1.26)	NR	NR	NR	29.0	10.0	16.0	58.0	0.0	0.0	NR	3.2	0.0	0.0
				Semaglutide 2.4 mg/week (n = 31)	− 1.8 (SE 0.16)	NR	− 5.1% (SE 1.26)	NR	NR	NR	16.0	3.0	6.0	32.0	0.0	0.0	NR	0.0	3.0	3.0
				Cagrilintide 2.4 mg/week (n = 30)	− 0.9 (SE 0.15)	NR	− 8.1% (SE 1.23)	NR	NR	NR	13.0	0.0	7.0	33.0	0.0	0.0	NR	6.7	3.0	0.0
BI456906 [1,3,4,5] (NCT04153929)	2	Adults (age ≥ 18 y), T2D, HbA1c 7.0–10.0%, BMI 25–50 kg/m^2, on metformin	16 weeks	BI456906 2.7 mg/week (n = 50)	− 1.67 (SD 0.78)	NR	− 6.68% (SD 4.05)	46.0	16.0	NR	46.0	26.0	14.0	NR	NR	0.0	NR	NR	NR	NR
				BI456906 1.8 mg twice a week (n = 49)	− 1.79 (SD 0.76)	NR	− 8.95% (SD 5.33)	57.1	34.7	NR	46.9	22.5	22.5	NR	NR	0.0	NR	NR	NR	NR
				Semaglutide 1 mg/week (n = 50)	− 1.50 (SD 0.84)	NR	− 5.40% (SD 4.33)	38.0	16.0	NR	12.0	4.0	10.0	NR	NR	0.0	NR	NR	NR	NR
				Placebo (n = 59)	− 0.23 (SD 0.81)	NR	− 1.20% (SD 3.52)	6.8	0.0	NR	8.5	5.1	11.9	NR	NR	1.7	NR	NR	NR	NR

1 Only the data from slow escalation regimens of retatrutide presented here for clarity

2 One case of acute cholecystitis in the 8 mg fast escalation group

3 Supraventricular arrhythmias and cardiac conduction disorders were not significantly greater in the intervention groups

4 One cholecysitis in a patient when on 0.06 mg/week

5 Only the data from highest once a week and twice a week doses of BI456906 reported for clarity

SAR425899 treatment not reported). The trial to evaluate SAR425899 in the treatment of NASH (NCT03437720) has been withdrawn (due to reasons not related to safety concerns).

A phase 2 study investigating BI456906, a GLP-1/GCGR dual agonist, in adults with T2D inadequately treated with metformin showed that at 16 weeks follow-up, compared to placebo, BI456906 1.8 mg twice a week subcutaneous injection achieved significantly greater HbA1c reduction (1.79 [SD 0.76]% vs. 0.23 [SD 0.81]%, $p < 0.0001$) and relative weight reduction from baseline (8.95 [SD 5.33]% vs. 1.20 [SD 3.52]%, $p < 0.0001$). In the same study, semaglutide achieved HbA1c reduction by 1.50 [SD 0.84]% and relative weight reduction of 5.4 [SD 4.33]% (statistics for BI456906 and semaglutide comparison not reported).

Unlike GLP-1 or GIP receptors, glucagon receptors are expressed in abundance in the liver. Therefore, there is greater focus on the fatty liver related benefits with glucagon-based therapies. An improvement in fatty liver disease with a comparable glucose improvement to other incretin agents will be of value in clinical practice.

Other Dual Agonists

CagriSema is a novel dual agonist that combines a GLP-1RA (semaglutide) with a long-acting amylin analogue (cagrilintide). In a phase 2 study among adults with T2D and BMI > 27 kg/m^2, treatment with CagriSema (semaglutide 2.4 mg/cagrilintide 2.4 mg) once a week subcutaneous injection over 32 weeks resulted in greater HbA1c reduction (− 2.2 [SE 1.5]%) compared to cagrilintide monotherapy (0.9 [SE 0.15]%) (estimated treatment difference 1.3%, $p < 0.0001$) and greater weight reduction from baseline compared to both active controls (CagriSema, − 15.6 [SE 1.26]%; semaglutide, − 5.1 [SE 1.26]%; cagrilintide, − 8·1 [SE 1·23]%) [53]. However, participants randomized to CagriSema treatment had shorter duration of diabetes which may have influenced the results. CagriSema has now entered series of phase 3 trials (REDEFINE program). REDEFINE-2 is evaluating its use in people with overweight/obesity and T2D with primary outcome being weight reduction and one of the secondary outcomes being HbA1c reduction (NCT05394519).

Several other dual agonists are in the pipeline. Maridebart-cafraglutide (AMG133) is an antibody–drug conjugate. It has an IgG immunoglobulin which inactivates GIPR and two GLP-1 analogue moieties. Interestingly, unlike GLP-1/GIPR dual agonists, maridebart-cafraglutide produces GIPR antagnosim and GLP-1 agonism. Preclinical studies had shown promising effects in improving glycaemia and weight [54]. A phase 2 clinical trial is currently underway evaluating its role in the treatment of adults with obesity, with or without T2D and is expected to be completed by 2025 (NCT05669599). Developing on potential for weight loss and glucose control with amylin and calcitonin, dual amylin calcitonin receptor agonists (DACRA) have been studied in the treatment of T2D. LY3541105, a DACRA with an amylin backbone, is likely to enter human studies soon. Another group of DACRAs with a salmon calcitonin backbone (known as KBPs) have shown strong weight and glucose reducing effects in animal models with obesity and diabetes either alone or in combination with GLP-1 receptor agonists [55]. HEC88473 is an Injectable GLP-1/FGF21 co-agonist hybrid peptide. It has completed phase 1 trials for the treatment of T2D and overweight/obesity (NCT05943886) as well as of NASH (NCT04829123).

GLP-1/GIP/GCGR Triagonists

Retatrutide is the first triagonist that entered clinical trials. In a phase 2 RCT among adults with T2D and BMI over 25 kg/m^2, retatrutide (4, 8, or 12 mg once weekly subcutaneously) achieved dose-dependent HbA1c reduction by up to 2.02 [SE 0.11]%, which was superior to placebo and dulaglutide 1.5 mg once weekly (1.41, [SE 0.12]%) at 36 weeks of follow-up [56•]. Similarly, retatrutide yielded a dose dependent weight reduction by up to 16.94 [SE 1.30]% which was superior to that achieved with dulaglutide 1.5 mg once a week (2.02, [SE 0.72]%). It is noteworthy that, like other GLP-1RAs and dual agonists, retatrutide-induced weight loss is less among people living with T2D compared to those without. For instance, in a phase 2 trial investigating retatrutride for obesity without T2D, weight loss from baseline by 48 weeks in the group treated with retatrutide 12 mg once a week was 24.2% (95% CI, − 26.6 to − 21.8) [57]. Furthermore, higher dose dulaglutide (up to 4.5 mg once a week), semaglutide and tirzepatide can yield greater HbA1c and weight reduction than dulaglutide 1.5 mg weekly and head-to-head comparisons against those agents have not been made. A series of phase 3 clinical trials are on-going investigating retatrutide in the treatment of adults with type 2 diabetes and overweight/obesity adults (TRIUMPH 2 [NCT05929079]), obesity and obstructive sleep apnoea (without diabetes) (TRIUMPH 1 [NCT05929066]), class III/IV obesity with cardiovascular disease (TRIUMPH 3 [NCT05882045]), and obesity with knee osteoarthritis (TRIUMPH 4 [NCT05931367]). Other triagonists in development are summarized in Table 1.

Safety

Gastrointestinal effects are the commonest adverse events noticed with incretin-based therapies: nausea (15–30%), vomiting (10–15%), and diarrhea (5–10%) [58]. These are dose-dependent, manifest during treatment initiation or escalation, and often dissipate over time. Incidence

varies with background treatment (higher with metformin and insulin) and therefore not necessarily comparable across studies. Compared to placebo, GLP-1RA are 2.5–3.8 times more likely to be discontinued due to gastrointestinal adverse events [59]. Nausea and vomiting are more likely related to the direct effects on brainstem, than to delay in gastric emptying [8••]. In a meta-analysis of published randomized controlled trials, incidence of nausea (13.9–22.6%), vomiting (5.4–10.2%), diarrhea (13.3–19.2%), and treatment discontinuation due to adverse events (7.3–10.2%) was greater with all doses of tirzepatide compared to placebo and was dose-dependent [60]. In phase 2 studies, tirzepatide 15 mg once a week and retatrutide 12 mg once a week had comparable gastrointestinal adverse event profile to their active comparators, semaglutide 1 mg once a week and dulaglutide 1.5 mg once a week, respectively. In contrast, cotadutide 300 mcg once a day, CagriSema (2.4 mg/2.4 mg) once a week and BI456906 1.8 mg twice a week caused more gastrointestinal adverse events than liraglutide 1.8 mg once a day and semaglutide 1 mg once a week and semaglutide 1 mg once a week, respectively (Table 2). A significant risk of gallstones, cholecystitis, or pancreatitis was not observed with tirzepatide, retatrutide or BI456906 and was not reported with cotadutide. It should be noted that all poylagonists achieved superior HbA1c and weight improvements compared to GLP-1RA comparators.

Injection site reactions (itching, rash, erythema) have been reported with all GLP-1RAs, affecting 1–20% of the patients, often mild and transient, commoner with long-acting preparations, and with more immunogenic agents [61, 62]. However, the incidence was relatively low with polyagonists (e.g., retatrutide [2–4%], tirzepatide [3–4%]) [56•, 63]. An increased risk of worsening diabetic retinopathy was noted in SUSTAIN-6 trial, the cardiovascular outcome study with injectable semaglutide (OR 1.75, 95% CI 1.10–2.78), but not with any other GLP-1RAs [64]. Similar risk has not been observed with tirzepatide [65], and outcomes have not been reported with other polyagonists thus far. An increase in heart rate (1.86 beats per minute [95% CI 0.85–2.87]) has been reported with GLP-1RA [61], but without an increase in risk of atrial fibrillation [66]. Similar observations were made with tirzepatide [41] and retatrutide [56•], and their clinical significance remains unclear.

Reassuringly, in any of the studies, serious adverse events with polyagonists were not greater than placebo or active comparators. No new safety signals have been identified. Overall, the gain in superior glycaemic and weight improvements appear to outweigh the rise in adverse effects. However, all these safety data on polyagonists are from relatively short-term studies while longer-term studies are awaited.

Future Perspectives

Impact and Challenges

A decade ago, weight and glucose improvements achieved by bariatric surgery were far superior to any pharmacological intervention. However, polyagonists have substantially narrowed this gap [57]. It is noteworthy that weight loss achieved with incretin-based pharmacotherapies has been lower among people with T2D compared to those without, and this stands true for polyagonists as well. Reason for this observation is not fully understood. Polyagonists have surpassed the weight reduction benefits of all pre-existing diabetes therapies with superior or non-inferior glucose improvements. Importantly, these were achieved with no serious adverse events or new safety signals. Improvements in liver, kidney, and cardiovascular co-morbidities are the other advantages.

Development of polyagonists is not without challenges. Firstly, heterogeneity between animal models and humans in the physiology and pathophysiology of these hormones makes it challenging to forecast pharmacodynamics, pharmacokinetics, efficacy, and safety of these agents in humans. For an example, unexpected adverse events (tachycardia and reticulocytopaenia) due to off-target toxicity led to discontinuation of GLP-1/GCGR dual agonist NN1177 development [67]. Secondly, peptide-based therapies being macromolecules can be immunogenic; a phenomenon observed with exenatide. This is likely due to less homology to human GLP-1 sequence. In fact, antibody formation against other GLP-1RA has been much rarer. Nevertheless, it does not seem to affect efficacy even among those with high antibody titres [68]. In the phase 2b RCT, 60.8% of the individuals exposed to cotadutide developed anti-drug antibodies, but it did not impact the efficacy. Seroconverted individuals had a higher incidence of injection site reactions, but the severity was not any worse [50•]. Treatment emergent antibody development was much less common with retatrutide (8.1%) [56•]. Thirdly, structural homology of some peptides and overlapping receptor repertoire (e.g., GLP-1 and GIP), poses further challenges in balancing agonistic effects to optimize synergistic benefits [69]. For example, [DA2]GIP-Oxm and [DA2] GLP-1/GcG significantly decreased body weight but YAG-glucagon did not [14]. This is possibly because the latter had more affinity to GIP receptor. Benefits of polyagonist as monotherapy, first-line therapy, and add-on treatment, their safety and efficacy in special populations (people with kidney/liver/heart disease), global accessibility, and cost-effectiveness compared to other existing pharmacological and surgical interventions are some of the other barriers to overcome.

Precision Medicine

Advances in genetic epidemiology (to identify patients at risk), pharmacogenomics (to identify patients' likelihood of responding to treatment), and biomarker discovery (to predict future disease risk and monitor progression) hold the future of precision medicine.

Availability of diverse treatment options, heterogeneity in treatment response, and predictors of response to treatment are fundamental requirements for its application. Although there are several classes of medication for glucose lowering, heterogeneity in glycaemic response is only modest [70]. However, GLP-1RA group showed significant intra-class heterogeneity in glycaemic response. Effect of liraglutide on cardiovascular and renal risk factors is also heterogeneous [71]. Several gene mutations [72, 73•], mRNA signatures [74] and gut microbial signatures [75] have shown to predict differences in glycaemic and weight response to liraglutide. The genes involved, often code for GLP-1 receptor or proteins involved in post-receptor signalling mechanism, beta cell function or tissue insulin sensitivity. In observational studies, several clinical and biochemical markers (largely reflecting residual beta cell function) proved to be predictive of greater glycaemic response to GLP-1RAs [76, 77]. It is noteworthy that there has been no uniform definition of "response to treatment" [78] and comparison of two arbitrarily defined responder and non-responder groups is not without caveats [79].

Increasing number of polyagonists are in development and these appear to have heterogeneous effects on improving glucose, weight, fatty liver, etc. Genetic risk predictors of fatty liver disease [80], atherosclerosis [81], and diabetic kidney disease [82] have been described. Clinical and biomarker defined phenotypes that predict specific complications have been reported [83]. Higher fasting GIP levels were associated with increased risk of cardiovascular disease [84]. It will be relevant to explore if specific polyagonists have unique advantages in primary and secondary prevention of these complications among patient with T2D who also possess genetic signatures predictive of such diseases. Clinical trials are increasingly being designed to determine efficacy of medications in specific sub-populations and these should inform the decision-making in matching the right medication to the right patient [85]. Individualizing the treatment strategy should also take in to account the patient's preferences (choice of oral vs injectable preparations, frequency of injections, etc.), co-morbidities, and affordability.

Conclusions

Development of polyagonists targeting multiple pathogenic mechanisms of T2D and co-morbidities is a rapidly evolving field. They have the potential to match the benefits of bariatric surgery. While several polyagonists have entered phase 3 studies and cardiovascular outcome trials, novel polyagonists, enteral preparations, and non-peptide agonists of peptide hormone receptors are the potential new developments in the pipeline. Availability of diverse agents and their unique efficacy/safety profiles necessitates the clinician to carefully individualize the treatment.

Abbreviations ALT: Alanine transaminase; AST: Aspartate aminotransferase; CCK: Cholecystokinin; CCKR: Cholecystokinin receptor; CI: Confidence interval; CKD: Chronic kidney disease; DACRA : Dual amylin calcitonin receptor agonists; DBP: Diastolic blood pressure; GCGR: Glucagon receptor; GIP: Glucose-dependent insulinotropic peptide; GIPR: GIP receptor; GLP-1: Glucagon-like peptide; GLP-1R: Glucagon-like peptide receptor; GLP-1-RA: GLP-1 receptor agonist; HFpEF: Heart failure with preserved ejection fraction; HR: Hazard ratio; hsCRP: High sensitivity C-reactive protein; LDL: Low density lipoprotein; MACE: Major adverse cardiovascular events; NASH: Non-alcoholic steatohepatitis; OR: Odds ratio; RCT: Randomized controlled trial; SBP: Systolic blood pressure; SD: Standard deviation; T2D: Type 2 diabetes

Author contributions NPS developed the research question, search strategy and outline of the review article and critically reviewed the manuscript . HAD conducted the literature review, wrote the first draft of the manuscript, prepared tables and figures. Both authors read the submitted manuscript.

Declarations

Competing interests The authors declare no competing interests.

Conflict of Interest Nothing to declare.

Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Ethics Approval Not applicable.

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