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REVIEW

Contemporary Classification of Glucagon-Like Peptide 1 Receptor Agonists (GLP1RAs)

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ABSTRACT

This communication provides a contemporary classification of glucagon-like peptide 1 receptor agonists (GLP1RAs) based on indication, route, and frequency of administration, which could support a person-centric approach to treatment choice. It includes all recently developed GLP1RAs as well as those in advanced stages of clinical study. Keeping pace with current trends in pharmacology and metabolic medicine, it attempts to bring clarity and simplicity to a complex spread of information.

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Key Summary Points

This review summarizes the latest developments in GLP1RA therapy for the management of diabetes and obesity.

All recently developed GLP1RAs, as well as those in advanced stages of clinical study, are described.

In addition to GLP1RA monotherapies, various additional GLP-1RA co-administration strategies are discussed, citing the most recent evidence available for them.

A contemporary classification of GLP1RAs based on indication, route, and frequency of administration is also provided.

INTRODUCTION

The glucagon-like peptide 1 receptor agonists (GLP1RAs) are a modern, rapidly evolving class of drugs for which there are an increasing

number of indications. GLP1RAs were originally only available as injectable therapies for the glycaemic management of type 2 diabetes mellitus (T2DM), but they are now also available in oral formulations, such as oral semaglutide, in several countries. These molecules are currently being studied in relation to their possible use for various other indications, such as for cardiovascular risk reduction in T2DM, for weight reduction in obesity, for nonalcoholic steatohepatitis (NASH), and for Alzheimer's. Recent advances in GLP1RA pharmacology have created a need to revisit the classification of this class of drugs. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EARLIER CLASSIFICATIONS

Earlier taxonomic frameworks were based on the structure of the GLP1RA (exendin-based and human glucagon-like peptide-1 (GLP-1)). However, this taxonomic basis does not aid clinical decision making. The recent expansion in indications for the administration of GLP1RAs is not reflected in earlier classification schema. The South Asian Task Force provides consensus recommendations on the use of GLP1RAs; it classifies GLP1RAs according to their duration of action into short, intermediate, long, and continuous acting.

IDEAL CLASSIFICATIONS

An ideal taxonomic structure should help the user in his or her daily work. For a student of pharmacology, for example, an ideal classification should describe drug pharmacokinetics and dynamics. For the clinician, a rubric should assist with the appropriate use of the concerned drugs. A person-centric approach, crafted with the person seeking medical care in mind, is perhaps the best way to craft and organize a drug classification system.

GLP1RAs have been listed as acting on fasting, postprandial, or both forms of hyperglycaemia. This approach has, however, been criticized for being myopic and oversimplistic. While duration of action is a pharmacological contract, frequency of administration is person-oriented, and has been used to create a person-centred taxonomy for GLP1RAs [1].

CONTEMPORARY CLASSIFICATION

We suggest a contemporary classification scheme for GLP1RAs that incorporates drug indication, route of administration, and frequency of administration. This GLP1RA classification is concordant with the thought process and conversational flow of a typical patient–provider interaction: determine the indication, achieve agreement on the preferred route of administration, and then choose from various options.

Some GLP1RA preparations have been withdrawn from the market while others are in advanced stages of development. We have chosen to include these for the sake of completeness. GLP1RAs are also available as co-formulations with insulins, and are being studied as co-formulations with other peptide agonists. These, too, are included in this review to ensure comprehensive coverage.

Table 1 summarizes the proposed classification based on route and indication. We hope that this person-centric, reader-friendly classification of GLP1RA will benefit students, clinicians, and researchers alike.

CLASSIFICATION OF GLP1RAS BASED ON INDICATION

Broadly speaking, we can classify GLP1RAs based on whether they are indicated for (or, if the GLP1RA is in the development phase, intended for) T2DM or for obesity.

GLP1RAs for the Treatment of T2DM

GLP1RAs are becoming a popular treatment option for people with T2DM due to their multiple benefits, such as their ability to lower glycated haemoglobin levels and reduce weight and their low risk of causing hypoglycaemia

Table 1 Contemporary classification of glucagon-like peptide 1 receptor agonists (GLP1RAs)

Route/indication	Type 2 diabetes mellitus	Obesity
Monoformulations		
Oral	Semaglutide 3, 7, 14 mg	Semaglutide 50 mg;[a]
	Semaglutide 25, 50 mg[a]	Danuglipron[a]
	Danuglipron[a]	
Subcutaneous daily	Lixisenatide; liraglutide 0.6–1.8 mg; exenatide BD	Liraglutide 3.0 mg
Subcutaneous weekly	Exenatide LAR; dulaglutide; semaglutide 0.25–1.0 mg; albiglutide[b]	Semaglutide 2.4 mg
Implantable	ITCA 650[b]	
Co-formulations		
Route/content	GLP1RA + insulin	GLP1RA + other agonist
Daily subcutaneous	IDegLira; LixiLan	
Weekly subcutaneous	IcoSema[a]	Sema-Amylin[a]
		HM15211[a]
		Tirzepatide 5, 10, 15 mg[c]

[a] In development
[b] Discontinued
[c] Being tested for both type 2 diabetes mellitus and obesity

(Table 2). Apart from these advantages, cardiovascular outcome trials (CVOTs) of GLP-1RA conducted over the years have established the cardiovascular (CV) safety of GLP1RAs, as they are noninferior to placebo in cardiovascular outcomes, whereas some GLP1RAs such as liraglutide have shown CV superiority over placebo in reducing three-point major adverse cardiovascular events (MACEs) [2]. Despite their shared overall mechanism, a wide range of clinical results and pharmacodynamics are shown by GLP1RAs because they vary significantly in structure and pharmacokinetics [3]. In this review, we attempt to describe each briefly from the clinician's point of view.

Exenatide Injection BID

Exendin-4 is a peptide present in the saliva of the Gila monster [4]. Exenatide is a synthetic form of exendin-4 that has 50% sequence homology with the native GLP-1 hormone. It was first approved in 2005 for the treatment of T2DM. Substitution of the amino acid arginine with glycine at position 2 makes exenatide resistant to the enzyme dipeptidyl peptidase-4 (DPP-4) and provides a half-life of around 2–4 h [5]. A twice-daily dose regime administered 60 min before breakfast and dinner caused glycated haemoglobin (HbA_{1c}) levels to drop by approximately 1.0% over 30 weeks and a weight loss of 1.0–2.5 kg over 16–30 weeks [6]. Exenatide once-weekly also led to a 12% reduction in triglyceride, a 6% reduction in low-density lipoprotein C (LDL-C), and a 24% increase in high-density lipoprotein C (HDL-C), resulting in an overall improvement in the lipid profile [7]. A systemic review found that exenatide and insulin produced similar reductions in HbA_{1c}, but in terms of weight reduction, exenatide excelled over insulin by inducing a loss of 3–6 kg at 52 weeks of follow up. Although hypoglycaemia rates were similar with exenatide and insulin, placebo-controlled trials have shown that nausea is a major adverse event in patients treated with exenatide [6]. Increasing the dose of exenatide in patients with an estimated glomerular filtration rate

(eGFR) of 30–60 mL/min/1.73 m^2 is not recommended, and it is contraindicated in patients with an eGFR of less than 30 mL/min/1.73 m^2.

Exenatide Extended Release (ER) QW

A sustained-release formulation of exenatide consisting of microspheres of exenatide and a biodegradable medical polymer was developed as an exenatide once-weekly injection. Exenatide QW has been shown to produce a significantly greater reduction in HbA_{1c} than exenatide BID, whereas weight reduction benefits and hypoglycaemic event rates were comparable [4]. Since exendin-4 is a foreign element used in the development of exenatide, it is expected to cause antibody formation in humans. A post-hoc analysis confirmed that there was low-titre antiexenatide antibody formation in humans with both exenatide BID and exenatide QW, but this had no effect on the efficacy of exenatide. However, higher-titre antibody formation—a less common phenomenon—leads to a significant reduction in the average efficacy of exenatide QW [8].

Lixisenatide

The exendin-4-based GLP1RA lixisenatide has a half-life of 2–3 h with a once-daily dose injection regimen [9]. The GetGoal clinical trial programme for lixisenatide showed that HbA_{1c} was lowered by up to 0.9%, and there was a marked reduction in postprandial glucose (PPG), probably due to the delaying effect of lixisenatide on gastric emptying [10]. In terms of weight loss, lixisenatide induced a reduction of 1–3 kg [11]. Since it is derived from a foreign peptide, antibody production after the administration of lixisenatide to patients is frequently seen [9].

Liraglutide

Liraglutide—administered as a once-daily injection—is a GLP1RA with two minor structural differences from endogenous glucagon-like peptide-1 (GLP-1) that lead to 97% homology with the GLP-1 sequence. A C-16 fatty acid is attached with the help of a glutamine spacer to the lysine at position 26 in the amino acid chain, and the lysine at position 34 is replaced with arginine. These minor structural changes lead to a half-life of 13 h, slow dissolution of liraglutide from the injection site, increased binding to albumin, and reduced inhibition by DPP-4 [12]. The immunogenic reaction (the development of antiliraglutide antibodies) induced by liraglutide is less than that induced by exenatide and has no impact on its efficacy and safety [13]. The Liraglutide Effect and Action in Diabetes (LEAD) programme, which focused on the effects of liraglutide at doses of 1.2 and 1.8 mg, demonstrated the superiority of this GLP1RA for glycaemic control and weight loss compared with active comparators or placebo. Liraglutide also reduces the systolic blood pressure (SBP) and improves beta-cell function and the lipid profile [14]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) CVOT trial showed the superiority of liraglutide by noting that its use yielded a 13% MACE reduction [15].

Once-Weekly Semaglutide (Semaglutide QW)

Semaglutide is an acylated GLP1RA, like liraglutide. It has 94% homology with GLP-1. It differs from GLP-1 in two amino acids (α-aminoisobutyric acid (Aib) at position 8 and arginine at position 34) and the addition of a C-18 diacid to the lysine at position 26, which allow the utilization of semaglutide as a once-weekly injectable therapy [16]. The phase 3a clinical development programme SUSTAIN established the superiority of semaglutide for HbA_{1c} reduction and weight reduction in comparison to placebo as well as active comparators [17]. SUSTAIN 6, a CVOT of semaglutide QW, confirmed its cardiovascular safety as well as noting a significant (26%) reduction in MACEs [18]. SUSTAIN 1–5 did not find an increase in diabetic retinopathy (DR) events with semaglutide QW use, but a significantly increased (by 76%) risk of DR was seen in the SUSTAIN 6 trial [19].

Dulaglutide

Dulaglutide, a GLP1RA with a half-life of 4 days, comes as a once-weekly dosage injection. Its ability to bind with human IgG4 keeps it

protected from proteolytic degradation by DPP-4. Moreover, its high molecular weight (57 kDA) prevents its renal clearance and extends its half-life [20]. Compared with controls such as placebo, metformin, and liraglutide, dulaglutide results in significant reductions in HbA_{1c} and fasting plasma glucose (FPG), a similar risk of hypoglycaemia, and less body weight loss when used as a monotherapy [21]. In all phase 3 studies of dulaglutide (the AWARD studies), dulaglutide enabled significantly more patients to achieve their HbA_{1c} targets than when other comparators (except liraglutide) were used [22]. A MACE reduction of 12% was reported from a CVOT of dulaglutide (REWIND) [23].

Albiglutide

Another long-acting GLP1RA with once-a-week dosing, albiglutide is a GLP-1 dimer bound to albumin and has notable DPP-2 resistance. This agent produces fewer gastrointestinal tract (GIT) side effects than other comparable GLP1RAs and is safe in patients with renal failure. In comparison to several other GLP1RAs, it produces a smaller improvement in HbA_{1c}: up to 1%. Its weight reduction benefits are also less profound compared to other GLP1RAs [24]. This could be due to its relatively large molecular weight and reduced central nervous system (CNS) penetration [25].

Oral Semaglutide

Semaglutide, a novel once-daily GLP-1 receptor agonist given orally as a tablet. The tablet formulation includes an absorption enhancer, sodium *N*-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC). This formulation was recently approved for the treatment of patients with T2DM [16]. The Peptide Innovation for Early Diabetes Treatment (PIONEER) clinical trial program investigated 3, 7, and 14 mg doses of oral semaglutide, with 3 mg used as the initial dose and 7/14 mg as the maintenance dose. In those studies, oral semaglutide provided significantly better efficacy than placebo and commonly used glucose-lowering medications, including DPP-4 inhibitors such as sitagliptin, sodium-glucose co-transporter-2 inhibitors (SGLT2is) such as empagliflozin, and the subcutaneous GLP1RAs liraglutide and dulaglutide. An event-driven pre-approval CVOT, PIONEER-6, showed that there was a 21% reduction in MACEs (noninferior) with oral semaglutide [26]. The efficacy and safety of high-dose (25 and 50 mg) oral semaglutide are currently being compared with those of 14 mg oral semaglutide in an ongoing phase 3b trial. This trial proposed to enrol 1224 people with T2DM who were previously treated with other oral antidiabetic medicines; it has a duration of 68 weeks and is expected to end by March 2023 [27].

Danuglipron

Danuglipron was developed in an attempt to obtain a small-molecule oral GLP1RA that could be used in standard formulations and could therefore be combined with other oral therapies, unlike oral semaglutide [28]. A phase I study was conducted to assess the safety profile, pharmacokinetics, and pharmacodynamics of the drug. Results from the study showed that HbA_{1c} was reduced by 0.9%, 1.2%, and 1.2% at doses of 15, 70, and 120 mg, respectively, and that body weight was decreased by 4.0 kg (70 mg dose) and 7.9 kg (120 mg dose) after 4 weeks of treatment. The safety profile and tolerability of danuglipron were found to be similar to other GLP1RAs. Phase 2 clinical trials of this drug are ongoing [29].

ITCA 650

This is a miniature implantable device consisting of an osmotic pump system that maintains a continuous supply of GLP1RA by delivering subcutaneous exenatide at a constant preset rate for up to 12 months. Though invasive in nature, it provides freedom from repeated injection. However, its utility during illness, fasting, or unexpected changes in renal/hepatic parameters is thought to be one of its limitations [30].

Co-formulations

As T2DM is a chronic progressive disease leading to a gradual decline in β-cell function, treatment intensification through the use of a combination of drugs becomes necessary to

address multiple pathophysiological defects [31, 32]. Several clinical studies have shown that glycaemic control and weight gain can be improved without incurring a risk of hypoglycaemia by using basal insulin plus a GLP1RA; many such combinations are available and used [33], as described below.

GLP1RA and Insulin Combination Insulin is a logical partner for GLP1RAs, with an entirely complementary mode of action that leads to additive glucose reduction in subjects with T2DM. Therapies based on fixed-ratio combinations (FRCs) of a GLP1RA with basal insulin have been developed. Two insulin and GLP1RA co-formulated combinations have been approved to treat T2DM: lixisenatide–insulin glargine and liraglutide–insulin degludec. Both formulations produce robust glucose control, often without weight gain and with less hypoglycaemia than observed with insulin alone [34].

iGlar U-100/Lixisenatide 33 or 50 μg/ml (iGlarLixi) iGlar U-100/lixisenatide 33 or 50 μg/ml combinations used as a once-daily dose have been tested in LixiLan phase 2 and 3 trials. The studies demonstrated that iGlarLixi has superior efficacy for glycemic control and weight loss as compared to iGlar alone. Also, the risk of hypoglycaemia was not increased and the rates of nausea and vomiting were low in the iGlarLixi group [35].

Insulin Degludec 100 U/ml and Liraglutide 3.6 mg/ml (IDegLira) IDegLira is a fixed-ratio combination of basal insulin degludec 100 U/ml and liraglutide 3.6 mg/ml [36] that is administered as a once-daily injection at any time (albeit preferably at the same time) of the day. Improvements in both FBG and PPG along with reductions in hypoglycaemic events, weight gain, and nausea have been demonstrated in the DUAL I–VII trials. Therefore, this combination of ultralong-acting basal insulin and a GLP1RA utilizes the clinical benefits of both drugs [37].

IcoSema (Insulin Icodec350U/Semaglutide 1 mg) IcoSema (insulin icodec350U/semaglutide 1 mg) is a novel FRC of once-weekly (OW) basal insulin icodec and semaglutide. It is recommended for once-weekly administration, irrespective of meals, in order to improve patient adherence and outcomes. It is expected to have superior HbA_{1c} reduction compared to monocomponents, weight benefits compared to basal insulin, and a reduced risk of hypoglycaemia. The phase 3 development program COMBINE 1–3 is currently being conducted on this FRC [38].

GLP-1/GIP Receptor Dual Agonists Tirzepatide (formerly known as LY3298176) is a novel glucose-lowering medication that stimulates the receptors for both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. This 39-amino-acid peptide is based on the biologically active N-terminal GIP(1–14) sequence with an N2 aminoisobutyric acid substitution. The mid-sequence contains substitutions compatible with GLP-1 receptor agonism, and there is a C20 fatty diacid chain linked via glutamic acid to the Lys20 residue to facilitate attachment to albumin, prolonging viability in the circulation. There is also an amidated exenatide-like C-terminal sequence. The structure confers stronger agonism for the GIP receptor than the GLP-1 receptor: the binding affinity for the GIP receptor is similar to that of native GIP(1–42), but it is about fivefold weaker for the GLP-1 receptor than native GLP-1. This provides a degree of balance that takes account of the physiologically higher circulating concentrations of GIP than GLP-1. The modifications reduce enzymatic degradation and provide sufficient durability for once-weekly subcutaneous administration. Tirzepatide has been compared with placebo and other glucose-lowering medications such as once-weekly injectable semaglutide, insulin degludec, and insulin glargine in various trials of the phase 3 SURPASS clinical trial programme. Compared to placebo, tirzepatide was associated with dose-related mean reductions in HbA_{1c} of 1.00, 1.67, 1.83, and 1.89% with 1, 5, 10, and 15 mg doses, respectively [39]. In its cardiovascular outcomes trial, tirzepatide is being compared with dulaglutide 1.5 mg, which has a confirmed cardioprotective

effect. The study is expected to complete by 2024 [40].

GLP1RAs for the Treatment of Obesity

Obesity is a global challenge for which there are limited therapeutic options. Obesity is a chronic, multifactorial disease that can lead to complications such as cardiovascular diseases (CVDs), T2DM, sleep apnea, and malignancy [41]. Given emerging evidence of the involvement of an abnormal satiety and feeding centre within the brain, there is a need for the development of effective pharmacotherapies or antiobesity medications (AOMs) as an adjunct to lifestyle interventions [42]. While most approved AOMs induce moderate weight loss of up to 10% [43], the GLP1RA class of drugs and combinations that include them have promising weight reduction benefits (Table 2).

Semaglutide 2.4 mg QW

The STEP 1 clinical trial has investigated the benefits of once-weekly injections of semaglutide 2.4 mg in the management of people who are obese or overweight [44]. In a double-blind trial of 1961 nondiabetic obese ($\geq$ 30 kg/m^2) or overweight patients ($\geq$ 27 kg/m^2) with coexisting weight-related complications, semaglutide 2.4 mg along with lifestyle modifications led to a 14.9% reduction in body weight as compared with a 2.4% reduction with placebo, with an estimated treatment difference of − 12.4 percentage points at 68 weeks. The mean reduction in body weight from baseline to week 68 was − 15.3 kg in the semaglutide group as compared to − 2.6 kg in the placebo group. 86.4, 69.1, and 50.5% of the patients on semaglutide 2.4 mg achieved weight losses of 5% or more, 10% or more, and 15% or more, respectively, at the end of 68 weeks. Not only that, patients receiving semaglutide also reported significant improvement in cardiometabolic risk factors and physical functioning as compared to the placebo arm [44]. Transient nausea and diarrhoea were the most common adverse events; these were of mild-to-moderate severity that subsided over time [41–43]. The STEP 2 trial compared semaglutide 2.4 mg versus placebo and semaglutide 1 mg for weight management in a double-blind, double-dummy design in overweight and obese T2DM patients. At the end of 68 weeks, semaglutide 2.4 mg once a week demonstrated a superior and clinically meaningful decrease in body weight compared with placebo, with an estimated treatment difference of 6.2 percentage points (95% CI − 7.3 to − 5.2; $p < 0.0001$). A higher number of patients with semaglutide 2.4 mg versus placebo achieved a weight loss of 5% or more (OR − 4.88, 95% CI 3.58–6.64) [45]. Furthermore, semaglutide 2.4 mg has been investigated versus placebo as an adjunct to intensive behavioural therapy and a low-calorie diet for weight management in 611 overweight and obese patients in the STEP 3 trial. Higher proportions of the patients in the semaglutide 2.4 mg arm achieved weight losses of 5% or more, 10% or more, and 15% or more at the end of 68 weeks: 86.6, 75.3, and 55.8%, respectively [46].

Liraglutide 3 mg

Liraglutide 3 mg once-daily injection is approved as an AOM. The double-blind 56-week SCALE trial of 3,731 people without T2DM showed that liraglutide 3 mg induced a superior weight reduction of − 8% as compared to − 2.6% with placebo in 56 weeks [47]. While the weight loss benefits of liraglutide have been shown to be maintained for 2 years, patients are also able to tolerate the therapy, with only mild- to moderate-intensity adverse drug reactions (ADRs) relating to the GIT encountered [48]. A total of five randomized, placebo-controlled trials have been conducted to evaluate the efficacy and safety of liraglutide for weight management. Liraglutide 3 mg as an adjunct to diet and physical activity consistently resulted in a 4–6 kg weight loss, with higher proportions of patients achieving weight losses of at least 5 and 10% compared with placebo. The comparative data suggest that greater weight loss is achieved with liraglutide compared to orlistat or lorcaserin, but slightly lower weight loss than achieved with phentermine/topiramate [49].

Oral Semaglutide 50 mg

Oral semaglutide at a high dose of 50 mg will be examined in a phase 3a trial in the year 2021. With approximately 1000 obese or overweight subjects with comorbidities included in a 68-week-long study, this trial is designed to compare oral semaglutide and placebo in terms of efficacy and safety [50].

Danuglipron

Apart from its use in the management of T2DM, danuglipron has also been tested in obese and high-BMI patients for its weight loss benefits.

GLP-1 Co-formulations for the Treatment of Obesity

To achieve better weight-loss efficacy and mitigation of ADRs, combination therapies are now accepted in the management of obesity [51]. GLP1RAs can be combined with other compounds to target multiple signalling pathways involved in energy balance regulation.

GLP1RAs and Amylin Amylin, a peptide co-secreted with insulin from beta cells of the pancreas upon the ingestion of food, is known to regulate appetite, delay gastric emptying, and cause weight loss by acting on amylin receptors in the area postrema [52]. Rodent studies have shown that incremental administration of the amylin/calcitonin receptor agonist salmon calcitonin (sCT) along with liraglutide results in greater reductions in food intake, adipose tissue, and body weight compared to the individual drugs [53].

A novel once-weekly subcutaneous amylin analogue known as AM833 or cagrilintide has been tested in combination with semaglutide QW in diet-induced obese (DIO) rats and mice. In relation to the baseline body weight, DIO rats showed greater weight loss with the combination therapy than with each monotherapy [54]. A 20-week phase 1b RCT testing AM833 with semaglutide 1.2 mg/2.4 mg in overweight or obese patients proved that the combination is not only safe and well tolerated but that it also causes substantial weight loss, resulting in a mean percentage body weight reduction of 15–17% [55]. AM833 at a dose of 4.5 mg achieved weight loss of up to 10.8% when used as a monotherapy over 26 weeks. Whether it would be able to achieve greater weight loss relative to semaglutide if used as a monotherapy with longer exposure remains to be confirmed [56].

GLP-1/Glucagon Receptor Dual Agonists Glucagon, GLP-1, and oxyntomodulin (OXM) are transcription products of the proglucagon gene. Although all three peptide hormones have a similar source, they have different or opposite physiological roles, which makes them ideal candidates for development as co-agonists.

Apart from hyperglycaemia, glucagon receptor stimulation also leads to lipolysis as well as thermogenesis. These two effects would be beneficial for obese patients if glucagon receptor agonism could be performed in the presence of a counteracting drug such as a GLP1RA [57]. A rodent study of GLP-1/glucagon co-agonism demonstrated the restoration of leptin responsiveness in mice maintained on a high-fat diet, leading to 15% weight loss [58]. The beneficial effects of glucagon on body fat mass, nutrient intake, and energy expenditure are well documented from preclinical and clinical studies [59, 60]. Further, human phase 1 and 2 trials to investigate the actions of GLP-1/glucagon receptor dual agonists in obese patients are ongoing. GLP-1 and glucagon have also been used to selectively target G-protein-coupled receptors and to deliver steroid hormones as cargo to specific cell types in preclinical studies. Conjugation of GLP-1 with the glucocorticoid hormone dexamethasone produced striking weight loss through a combination of reduced food intake and increased energy expenditure in obese mice [61]. Peptides with GLP-1/glucagon co-agonist properties are listed in Table 3.

GLP-1/GIP Receptor Dual Agonists Another method of harnessing the catabolic effects of glucagon is to stimulate GIP receptors, which in turn stimulates glucagon secretion. However, this may enhance the diabetogenic potential of glucagon, which is involved in gluconeogenesis and glycogenolysis. Combining GIP with GLP-1

Table 2 Mean HbA_{1c} reduction and weight loss induced by each GLP1RA and their combinations

Drug	HbA_{1c} reduction (%)	Reference(s)	Weight reduction (kg)	Reference(s)
Exenatide BD	1/0.86	[6, 68]	1–2.5	[6]
Exenatide ER	1.28	[68]		
Lixisenatide	0.52	[69]	0.65	[69]
Albiglutide	0.66	[70]	0.26	[70]
Dulaglutide	1.38/1.18	[68, 70]	0.88	[70]
Liraglutide 1.8 mg	1.34/1.3–1.6	[14, 68, 71]	3.24	[71]
Liraglutide 3 mg			4–6	[49]
Semaglutide 1 mg	1.8/1.38	[17, 72, 73]	4.5–6.5	[17, 72]
Semaglutide 2.4 mg	0.5–1.6	[45, 46]	9.7–16.8	[45, 46, 74]
Oral semaglutide 14 mg	1.5–1.7	[75–79]	4.1–4.7	[75–79]
Tirzepatide	1.9–2.2	[80]	4–5.7	[80]

Table 3 Peptides with GLP-1/glucagon co-agonist properties that are under development [81]

Peptide	Proposed dose frequency	Developer
Preclinical phase		
IUB447	Daily s.c. injection	MB-2 LLC
MOD-6030/1	Weekly s.c. injection	Prolor/OPKO Biologics
VPD-107	Weekly s.c. injection	Spitfire Pharma
In phase 1 trials		
SAR 425899	s.c. injection	Sanofi
MEDI0382	s.c. injection	MedImmune
HM2525A	Weekly s.c. injection	Hamni Pharmaceuticals
ZP2929	Once-daily s.c. injection	Zealand and Boehringer Ingelheim
In phase 2 trials		
LY2944876/TT-401	Once-weekly s.c. injection	Eli Lilly
Not therapeutically useful		
Oxyntomodulin	Short-acting; $t_{1/2} \sim$ 12 min	

would not only reap the weight loss benefits of GLP-1 but also counteract the obesogenic potential of GIP. Potentiation of weight loss has been observed with the combination of GLP-1 and GIP, which shows that there is a distinct set of neurons for the action of GLP-1 and GIP in the ARN [62]. Tirzepatide at doses of 5, 10, and 15 mg is currently being investigated as an AOM in the SURMOUNT clinical trial programme. The SURMOUNT-1 trial is testing the ability of tirzepatide to produce weight loss in people who are overweight or obese. Participants are

randomized to tirzepatide at doses of 5, 10, or 15 mg, and the co-primary endpoints are the percent change in body weight and the proportion of people attaining at least a 5% reduction in their baseline body weight by week 72. The anticipated study completion date is May 2024 [63]. Tirzepatide has been found to be associated with a marked dose-dependent loss of body weight: a loss of 0.9 kg was observed with a dose of 1 mg, or 11.3 kg with a dose of 15 mg, whereas reductions of 2.7 kg with dulaglutide and 0.4 kg with placebo were noted. Over half of the patients receiving the 15 mg dose of tirzepatide developed antibodies to this agent, but these were generally of low titre and did not appear to compromise efficacy [64].

GLP-1/GIP/Glucagon Receptor Triple Agonists As discussed above, glucagon receptor stimulation has a role to play in weight loss by increasing energy expenditure. Combining the effects of GLP-1/GIP and glucagon receptor agonism in a single molecule might have the greatest impact on weight control. The GLP-1 action would cause a reduction in calorie intake and GIP stimulation would potentiate the incretin effect, which would neutralize the diabetogenic action of glucagon [65]. Weight lowering was particularly effective with some triagonists, which may be attributable to the inclusion of glucagon agonism: glucagon exerts a satiety effect and promotes energy expenditure. It is anticipated that the glucose-lowering effects conferred by the GLP-1 and GIP components of the triagonists more than compensate for the effect of glucagon receptor agonism in promoting endogenous glucose production. Further studies are awaited on this concept [66]. HM15211 consists of a novel long-acting glucagon, gastric inhibitory peptide, and glucagon-like peptide 1 (glucagon/GIP/GLP-1) receptor triple full agonist that is chemically conjugated with the constant region of human immunoglobulin via a nonpeptidyl flexible linker. A phase 1, first-in-human (FIH), single ascending dose (SAD) study to confirm the safety and tolerability profiles of HM15211 in healthy obese subjects was completed (NCT03374241) [67].

CONCLUSION

The present review represents a summary of the latest developments in GLP1RA therapy for the management of T2DM and obesity. Such developments help to improve patient outcomes and patient convenience (through the use of once-weekly dosage forms and oral formulations). In addition to GLP1RA monotherapies, various additional GLP1RA co-administration strategies have demonstrated benefits when used for the treatment of T2DM and obesity. To achieve comprehensive metabolic control, attempts have also been made to target other receptors in concurrence with GLP1RA using a single drug in the form of co-agonists or triple agonists. Advances in drug development and the rapidly expanding list of GLP-1-related drugs present a need to create a clinically relevant, pharmacology-based classification of these molecules. The present article fills this void and should remain relevant for the foreseeable future.

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