GLP-1 Receptor Agonists in 2026: From Glycaemic Control to Multisystem Therapeutics

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have rapidly evolved from glucose-lowering agents into multifaceted therapeutics with systemic clinical benefits. Originally inspired by the discovery of exendin-4 from Heloderma suspectum venom. These agents have undergone substantial pharmacological refinement to enhance half-life and therapeutic efficacy. Their mechanism of action centres on glucose-dependent insulin secretion, suppression of glucagon, delayed gastric emptying, and modulation of central appetite pathways, resulting in improved glycaemic control and significant weight reduction. Contemporary therapies include single agonists such as semaglutide and liraglutide, as well as dual incretin agents like tirzepatide, with emerging triple agonists and oral non-peptide formulations expanding the therapeutic landscape. Beyond metabolic control, GLP-1RAs demonstrate pleiotropic benefits, including reductions in cardiovascular events, renal disease progression, and systemic inflammation. Evidence also supports protective roles in respiratory, neurocognitive, and neuropsychiatric conditions, highlighting their potential as broad-spectrum disease-modifying agents. However, these benefits are accompanied by a range of adverse effects, most commonly gastrointestinal disturbances, as well as risks involving pancreatic, renal, ocular, and musculoskeletal systems. Rare but serious complications, including pancreatitis, diabetic retinopathy progression, and hypersensitivity reactions, necessitate careful patient selection and monitoring. The pipeline of next-generation therapies, including: dual, triple, and oral agents—suggests a paradigm shift toward increasingly personalised and multi-targeted treatment strategies. Despite their promise, challenges remain regarding long-term safety, accessibility, and the risks associated with unregulated compounded formulations. As of 2026, GLP-1–based therapies represent a cornerstone of modern metabolic medicine, with expanding applications that extend well beyond diabetes and obesity into multisystem disease management

1. History and Background

Obesity is a complex, multifactorial chronic disease that affects millions of individuals worldwide, many of whom also suffer from noncommunicable diseases such as type 2 diabetes mellitus [1]. Both conditions are associated with a decrease in life expectancy and the development of further pathological conditions [1]. Lifestyle changes, such as appropriate diet and regular exercise, have traditionally been prescribed as a means optimising adipose tissue metabolism and weight loss [2]. The addition of pharmacological therapies with properties that promote weight loss and reduce blood glucose levels represents a desirable approach in the management of obesity and T2DM. As such GLP-1RAs are increasingly being used to treat diabetes and obesity [3]. In 1990, John Eng isolated a native peptide from the venom of the Gila monster lizard, exendin-4, which is structurally similar, but possesses a longer half-life than the naturally occurring GLP-1 within the body [4]. This peptide competes with GLP-1 for its receptor, stimulating insulin secretion. The glucose lowering effects of exendin-4 was established through clinical trials . Following these discoveries, in 2005 the incretin exenatide became the first incretin analogue to be approved for the treatment of type 2 diabetes [5]. Following its approval many pharmaceutical companies focused their efforts on generating synthetic GLP-receptor analogues to treat type 2 diabetes that could augment and extend the relatively short half-life of GLP-1 [6] through modifications to amino acids and resisting cleavage by dipeptidyl peptidase-4 in vivo [4]. Glucose-dependent insulinotropic peptide (GIP) was the first incretin isolated [7]. GIP is synthesized in intestinal K cells and is enhanced in response to glucose or the ingestion of a meal [8].

Although GIP administration led to only modest changes in blood glucose levels in patients with type 2 diabetes, it exerts a prosurvival effect on beta cells in pancreatic islets [9]. When GIP was combined with synthetic GLP-1 receptor agonists, additive effects on both glucose levels and body weight occurred providing an even greater means of treating metabolic syndrome in those suffering from obesity [10]. GIP was also found to have very modest insulin sensitizing effects on adipocytes. Together, these efforts facilitated a new era of GLP-1 based therapeutics that now include double and triple agonists, several of which have been approved by international regulatory agencies, with more in the pipeline for the treatment of type 2 diabetes and obesity. Glucagon-like peptide-1 (GLP-1) receptor agonists are incretin analogues that promote glucose-mediated insulin release and glucose tolerance [11] and are primarily used in the treatment of type 2 diabetes mellitus and obesity. Therapies have included GLP-1 receptor agonists, dual-acting GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors have commonly been prescribed for years in the treatment of T2DM due to their impact on glucose control [12]. GLP-1 agonists are increasingly used for diabetes and weight loss, with several recognized complications, and emergency clinicians must be able to recognize and manage these complications [13].

2. Physiology and Mechanism of Action

The incretin family is generally considered to include GIP, GLP-1, and glucagon. Each of these incretins are produced and secreted by distinct cells namely K cells for GIP, discrete intestinal L cells for GLP-1 and pancreatic α-cells for glucagon, in response to meals . GLP-1 primarily stimulates the release of insulin form the pancreatic islets. GLP-1 agonists enhance and reproduce the effects of natural GLP-1. Ultimately during hypoglycaemia or when glucose levels are elevated such as after eating, GLP-1 is involved in the reduction of gastric emptying and food intake due to increased feelings of satiety. Moreover, it inhibits release of inappropriate post-meal glucagon, and has direct effects on the central nervous system (i.e., hypothalamus, nucleus accumbens, ventral tegmental regions, and vagus nerve) including hunger control and reducing inflammation.

3. Current Medication

The current medication approved for the treatment of type 2 diabetes mellitus and chronic weight management include:

1. Semaglutide: Available as a once-weekly subcutaneous injection for T2DM (Ozempic) or for weight loss (Wegovy), and as a daily oral tablet for the treatment of T2DM (Rybelsus).
2. Liraglutide: Administered as a once-daily subcutaneous injection for T2DM (Victoza) or for weight loss (Saxenda).
3. Tirzepatide: A dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (Mounjaro) approved for T2DM and weight loss.
4. Dulaglutide: A long-acting, once-weekly subcutaneous injection for T2DM (Trulicity).
5. Exenatide: Available as a twice-daily short-acting injection (Byetta) or a once-weekly extended-release injection (Bydureon) for T2DM.
6. Lixisenatide: A once-daily injection for the treatment of T2DM (Adlyxin).
7. Beinaglutide: A GLP-1 receptor agonist identified in clinical research as having potent effects on body weight and BMI reduction.

Table 1. showing current GLP-1 medication

Drug Name	Class / Mechanism	Indication(s)	Route of Administration	Dosing Frequency	Brand Name(s)
Semaglutide	GLP-1 receptor agonist	T2DM, Chronic weight management	Subcutaneous injection / Oral	Weekly (SC), Daily (oral)	Ozempic, Wegovy, Rybelsus
Liraglutide	GLP-1 receptor agonist	T2DM, Chronic weight management	Subcutaneous injection	Daily	Victoza, Saxenda
Tirzepatide	Dual GLP-1/GIP receptor agonist	T2DM, Chronic weight management	Subcutaneous injection	Weekly	Mounjaro
Dulaglutide	GLP-1 receptor agonist	T2DM	Subcutaneous injection	Weekly	Trulicity

Exenatide	GLP-1 receptor agonist	T2DM	Subcutaneous injection	Twice daily (IR), Weekly (ER)	Byetta, Bydureon
Lixisenatide	GLP-1 receptor agonist	T2DM	Subcutaneous injection	Daily	Adlyxin
Beinaglutide	GLP-1 receptor agonist	Investigational/limited clinical use (weight reduction)	Subcutaneous injection	Daily	—

4. Future and Experimental medications currently in the development phase

These treatment agents are currently in various stages of the clinical trial process and could one day form part of the medication use in the treatment of T2DM and obesity.

1. Retatrutide: A third generation "triple" agonist that targets GLP-1, GIP, and glucagon receptors.
2. Cagrilintide–semaglutide (Cagri-Sema): A once-weekly injection combining a GLP-1 receptor agonist with an amylin mimic.
3. VK2735: A dual GLP-1 and GIP receptor agonist being developed in both injectable and oral versions.
4. Orforglipron: A non-peptide, daily oral GLP-1 receptor agonist currently in Phase 3 trials.
5. Danuglipron: A daily oral chemical GLP-1 receptor agonist entering Phase 2 studies.
6. Amycretin: A dual GLP-1 and amylin agonist being developed as a once-daily oral tablet and subcutaneous injection.
7. Mazdutide (IBI362): A GLP-1 receptor agonist and glucagon mimic nearing Phase 3 completion.
8. Survodutide: A once-weekly injection that activates both GLP-1 and glucagon receptors.
9. Maridebart cafraglutide (MariTide): A monthly injectable designed to mimic GLP-1 while blocking GIP receptors.
10. Ecnoglutide (XW003): A once-weekly injectable GLP-1 receptor agonist.
11. GSBR-1290: An oral GLP-1 medication currently in Phase 2 trials.
12. ARD-101: An oral medication that activates intestinal bitter-taste receptors to trigger the release of GLP-1 and GLP-2.
13. APHD-012: A once-daily oral medication described as a distal jejunal-release dextrose bead.
14. Monlunabant: A once-daily oral cannabinoid receptor-1 inverse agonist.
15. Bimagrumab: A monthly intravenous monoclonal antibody against activin receptors.

Table 2. showing Future and Experimental GLP-1 medications currently in the development phase

Drug Name	Class / Mechanism	Development Stage	Route of Administration	Dosing Frequency	Key Features
Retatrutide	Triple agonist (GLP-1/GIP/Glucagon)	Phase 3	Subcutaneous injection	Weekly	Significant weight loss potential
Cagrilintide–semaglutide (CagriSema)	GLP-1 agonist + amylin analog	Phase 3	Subcutaneous injection	Weekly	Synergistic appetite suppression
VK2735	Dual GLP-1/GIP agonist	Phase 2	Oral / Subcutaneous	Daily / Weekly	Dual formulation approach
Orforglipron	Non-peptide GLP-1 agonist	Phase 3	Oral	Daily	First oral non-peptide GLP-1
Danuglipron	Small-molecule GLP-1 agonist	Phase 2	Oral	Daily	Oral alternative to injectables
Amycretin	GLP-1 + amylin agonist	Phase 2	Oral / Subcutaneous	Daily	Dual-hormone mechanism
Mazdutide (IBI362)	GLP-1 + glucagon receptor agonist	Phase 3	Subcutaneous injection	Weekly	Energy expenditure effects
Survodutide	GLP-1 + glucagon receptor agonist	Phase 3	Subcutaneous injection	Weekly	Targets obesity and NASH
Maridebart cafraglutide (MariTide)	GLP-1 agonist + GIP antagonist	Phase 2	Subcutaneous injection	Monthly	Long-acting, novel mechanism
Ecnoglutide (XW003)	GLP-1 receptor agonist	Phase 3	Subcutaneous injection	Weekly	Long-acting GLP-1 analog
GSBR-1290	GLP-1 receptor agonist	Phase 2	Oral	Daily	Oral peptide alternative
ARD-101	Gut-restricted small molecule	Phase 2	Oral	Daily	Stimulates endogenous GLP-1/GLP-2 release
APHD-012	Distal jejunal nutrient delivery agent	Early clinical	Oral	Daily	Mimics bariatric physiology
Monlunabant	CB1 receptor inverse agonist	Phase 2	Oral	Daily	Appetite suppression via endocannabinoid system
Bimagrumab	Anti-activin receptor monoclonal antibody	Phase 2	Intravenous	Monthly	Increases lean mass, reduces fat mass

5. Latest Clinical Benefits of GLP-1 Receptor Agonists

Glycaemic Control and Metabolic Management

GLP-1RAs have revolutionised type 2 diabetes mellitus management by effectively lowering blood glucose in a glucose-dependent manner, which minimises the risk of hypoglycaemia [14]. Trials such as DURATION-1 and SUSTAIN 3 demonstrated glycated haemoglobin

(HbA1c) reductions between 1.5% and 1.9% [4]. Furthermore, the dual agonist tirzepatide has shown even greater efficacy, reducing HbA1c by up to 2.0 percentage points, outperforming ultra-long-acting insulins [15]. Moreover, these medications inhibit inappropriate post-meal glucagon secretion and stimulate beta-cell pro-survival and proliferation mechanisms, helping to maintain islet cell mass over time [9]. Furthermore, at high dosages, (2.4 mg), semaglutide and tirzepatide have demonstrated the ability to reduce metabolic factors associated with liver disease, specifically reducing hepatic fibrosis and intrahepatic lipid content [12], [13].

Weight Management and Body Composition

Aside from the prominent impact GLP-1RAs have on the disease progression of type 2 diabetes mellitus, they have further been involved in facilitating significant weight loss through the enhancement of central satiety and delaying gastric emptying. Systematic reviews indicate that weight loss is primarily driven by a selective reduction in fat mass (approximately 17% at 3 months) and visceral adipose tissue. The STEP 1 trial demonstrated an average reduction in body weight of 14.9% with semaglutide administered at a dosage of 2.4 mg. Tirzepatide has shown even more substantial results, with weight loss ranging from 15% to 21% in the SURMOUNT-1 trial [4]. Unlike traditional caloric restriction, GLP-1 RAs appear to support skeletal muscle health by promoting glucose uptake via the AMP activated protein kinase pathway and mitigating muscle atrophy through the SIRT1 signalling cascade. These results seem to indicate that treatment with GLP-1Ras seem to create a more metabolically favourable ratio of skeletal muscle to visceral fat tissue (SMM/VAT) .

Cardiorenal Protection

Large-scale trials have established these agents as a critical means of reducing morbidity and mortality in high-risk patient groups. One such trial namely, the SUSTAIN 6 trial, tracked patients with preexisting cardiovascular, chronic kidney disease (CKD), or both. From this trial it had been demonstrated that parenteral administration with semaglutide once weekly resulted in a 26% reduction in Major Adverse Cardiovascular Events (a composite of death, nonfatal MI, and stroke). Moreover, the SOUL trial showed that oral semaglutide reduced cardiovascular event risk by 14%. GLP-1RAs improve microvascular blood flow, increase endothelial function, and reduce systemic vascular resistance and blood pressure. Moreover, these medications aid in slowing the progression to renal failure. In SUSTAIN 6, semaglutide was associated with a 36% reduction in new or worsening nephropathy and a nearly 50% reduction in macroalbuminuria [4]. As of January 2025, semaglutide is FDA-approved specifically for reducing kidney disease risk in T2DM patients [16].

Respiratory and Infectious Disease Benefits

Evidence suggests GLP-1 RAs provide protective effects against several systemic conditions. Use is associated with a reduced risk of COPD hazard ratio (HR) of 0.90, pneumonia (HR 0.84), and respiratory failure (HR 0.77). This may be due to reduced airway inflammation and improved protease balance. The medications are associated with a reduced risk of septicaemia (HR 0.83) and fewer deaths related to COVID-19 compared to placebo. There is

evidence of a reduced risk of inflammatory bowel disease (HR 0.88), likely due to the general anti-inflammatory properties of the incretin system [13].

Neuropsychiatric and Brain Health

Recent large-scale database analyses reveal that GLP-1 RAs possess broad pleiotropic effects on the central nervous system. There is a reduced risk of neurocognitive disorders (HR 0.95), specifically Alzheimer's disease (HR 0.88) and dementia (HR 0.92). This is thought to be due to reduced neuroinflammation, oxidative stress, and amyloid β deposition. GLP-1 RA use is associated with a significantly reduced risk of various addictions, including alcohol use disorder (HR 0.89), cannabis use disorder (HR 0.88), and opioid use disorder (HR 0.87). New data suggests a reduced risk of schizophrenia and other psychotic disorders, potentially due to the antipsychotic-like effects of GLP-1 activation observed in experimental models. As such, the use is associated with a reduced risk of seizures (HR 0.90) and schizophrenia/psychotic disorders (HR 0.82). Additionally, they appear to reduce the risk of suicidal ideation and intentional self-harm [13].

Next-Generation Multi-Pathway Agonists

As of late researchers have begun to move beyond single GLP-1 activation to "double" and "triple" agonists that target multiple metabolic pathways simultaneously. Novel Dual Agonists/Antagonists: Maridebart cafraglutide (MariTide) represents a unique approach; it mimics GLP-1 but blocks GIP receptors, with the potential for once-monthly dosing. Triple Agonists (GLP-1/GIP/Glucagon): Retatrutide has emerged as a potent third-generation agent. In a large phase 2 trial, it demonstrated superior glucose-lowering effects compared to dulaglutide and achieved profound weight loss of nearly 25% over 48 weeks. Amylin Combinations: Cagri-Sema, which combines the amylin mimic cagrilintide with semaglutide, is currently under development to further enhance weight loss and metabolic outcomes.

6. Adverse effects of GLP-1

However, despite the many beneficial qualities associated with GLP-1 Ras have also been associated with the development of adverse consequences such as: gastrointestinal complications, pancreatic and biliary disease, renal complications, ocular complications, musculoskeletal and body composition effects, hypersensitivity and dermatologic reactions, metabolic and systemic effects and risks of compounded and unregulated medications.

Gastrointestinal Complications

Gastrointestinal (GI) events occur in 40-70% of patients, typically appearing within the first eight weeks of treatment or during dose escalation. Common symptoms often include nausea (the most frequent), vomiting, diarrhoea, constipation, abdominal pain, dyspepsia, bloating, and flatulence [17]. Owing to the nature of this type of medication, these medications may cause gastroparesis and bowel obstruction due to their intrinsic action of slowing gastric emptying [18]. There is also an increased risk of gastroesophageal reflux disease (GERD), gastritis, and non-infectious gastroenteritis [19].

Pancreatic and Biliary Disease

GLP-1 RAs have been associated with an increased risk of drug-induced acute pancreatitis. While some trial data show no significant difference from placebo, large-scale database analyses and case reports suggest a distinct risk, particularly with agents like liraglutide [20]. Furthermore, GLP-1 RAs have been associated with increased risk of cholelithiasis (gallstones), cholecystitis, and cholangitis. This risk is higher at elevated doses, with longer treatment duration, and in patients experiencing rapid weight loss [21].

Renal Complications

Acute Kidney Injury (AKI), most cases of AKI are prerenal, caused by volume depletion and dehydration following severe GI losses (vomiting and diarrhoea). Although volume depletion from vomiting in some patients is the most common cause of AKI after GLP-1 RAs, these forms of medication can cause injury to the kidney via interstitial nephritis through drug-specific T-cell mediated hypersensitivity [22]. Furthermore, recent mapping data, suggests an increased risk of developing urinary stones [23].

Ocular Complications

Subcutaneous semaglutide and other GLP-1 RAs have been associated with the worsening of diabetic retinopathy, including vitreous haemorrhage and blindness [24]. This complication is most strongly linked to the rapidity and degree of HbA1c reduction during the first 16 weeks of therapy, particularly in patients with pre-existing retinopathy [25].

Musculoskeletal and Body Composition Effects

While weight loss is primarily fat-selective, it is consistently accompanied by a reduction in lean body mass. Importantly recent studies have shown a significant loss of bone mineral density in the femur and spine after one year of treatment, likely caused as a result of the enhanced bone resorption [26]. However, further research is needed on fracture-related outcomes in people living with obesity [26]. Patients have also reported increased instances of arthralgia, arthritis, tendinitis, and synovitis [27].

Hypersensitivity and Dermatologic Reactions

Injection site reactions, are common and typically minor, involving pruritus (the most common), warmth, and rashes . Severe allergic reactions such as anaphylaxis and angioedema have been reported, primarily with exendin-based therapies [28]. A further dermatological effect has been commonly referred to as "Ozempic Face", caused by a rapid loss of facial fat can lead to sagging skin and a prematurely aged appearance [29]. Other reactions are rare, but reports include bullous pemphigoid, alopecia, and panniculitis .

Metabolic and Systemic Effects

Hypoglycaemia, while the risk is low for the drug alone, it increases significantly when combined with sulfonylureas or insulin [30]. Diabetic Ketoacidosis (DKA): Rapid reduction or discontinuation of concomitant insulin when starting a GLP-1RA can precipitate DKA.

Hemodynamic Effects: Use is associated with an increased risk of hypotension and syncope, likely due to the drug's effect on blood pressure and volume status. General Well-being: Fatigue, dizziness, headaches, and sleep disturbances are frequently reported.

Risks of Compounded and Unregulated Medications

Due to global shortages, many patients use unregulated compounded versions, which carry specific dangers: Dosing Errors: Reports indicate up to 10-fold dosing errors, leading to prolonged severe GI symptoms. Contamination Risks: Unregulated facilities have been found using non-sterile sterilization methods (e.g., toaster ovens) or having unsanitary conditions, risking serious infections like fungal meningitis.

7. Comparison with other therapies

Compared to traditional therapies such as metformin and insulin, GLP-1 RAs offer additional benefits including weight loss and cardiovascular protection. When compared to SGLT2 inhibitors, GLP-1 therapies demonstrate complementary mechanisms, supporting combination approaches.

8. Future Directions

Future directions for GLP-1 RAs involve expanding their clinical applications, developing next-generation multi-pathway agents, and addressing critical gaps in long-term safety and health equity. Future investigations should evaluate GLP-1RAs as primary or adjuvant therapies for substance use disorders (including alcohol, opioid, cannabis, and stimulant use), psychotic disorders, and depressive disorders . Future research should aim to define the most effective combinations of pharmacotherapy and lifestyle interventions tailored to specific patient needs. This includes exploring sex-specific approaches, as female sex is associated with a greater weight loss response. Moreover, there is a critical need to adjust pricing and create distribution plans to ensure these medications reach underprivileged populations, who are often excluded from major clinical trials despite having higher rates of obesity and diabetes. Finally, legal and medical issues surrounding compounded formulations must be resolved to ensure patient safety and affordability without compromising the quality of the final product.

9. Conclusion

Taking all the research as a whole GLP-1Ras have undergone a remarkable transformation from targeted antihyperglycemic agents to cornerstone therapies with broad, multisystem clinical applications. Advances in molecular design and pharmacokinetics have enabled the development of long-acting, highly efficacious agents that not only improve glycaemic control but also produce substantial and sustained weight loss. The emergence of dual and triple agonists further underscores a shift toward integrated metabolic modulation, leveraging complementary hormonal pathways to optimise therapeutic outcomes. Beyond their metabolic effects, the expanding body of evidence supporting cardiovascular, renal,

neurocognitive, and anti-inflammatory benefits positions GLP-1–based therapies as disease-modifying agents with far-reaching implications. These pleiotropic effects are redefining treatment paradigms, particularly in patients with complex comorbidities such as obesity, type 2 diabetes mellitus, and cardiorenal disease. However, these benefits must be balanced against a well-characterised adverse effect profile, including gastrointestinal intolerance, potential pancreatic and biliary complications, and emerging concerns related to musculoskeletal and ocular health. Careful patient selection, dose titration, and longitudinal monitoring remain essential to maximise benefit while minimising risk. Looking forward, the therapeutic landscape is poised for continued expansion with the development of oral non-peptide agents, combination therapies, and novel receptor targets. These innovations promise improved accessibility, adherence, and individualisation of treatment. Nonetheless, challenges such as long-term safety data, cost, and the risks associated with unregulated compounded formulations must be addressed. In 2026, GLP-1 receptor agonists stand at the forefront of metabolic medicine, signalling a paradigm shift toward comprehensive, mechanism-based management of chronic disease.

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11. Addendum

GLP-1 RECEPTOR AGONISTS IN 2026

FROM GLYCAEMIC CONTROL TO MULTISYSTEM THERAPEUTICS

From a lizard venom discovery to a new era of multisystem, disease-modifying medicines

1990: Exendin-4 isolated from Heloderma suspectum venom inspired the development of GLP-1 receptor agonists.

Potent Glycaemic Control — Lower HbA1c by ~1.5–2.0% with low risk of hypoglycaemia

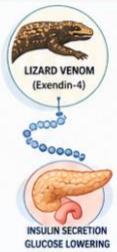
Substantial Weight Loss — 15–21% body weight reduction with tirzepatide

Cardiorenal Protection — Reduces CV events and slows kidney disease progression

Beyond Metabolism — Potential benefits in brain health, inflammation, respiratory disease & more

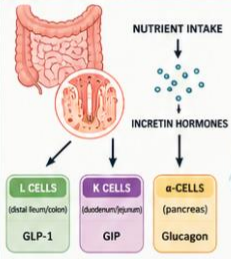
1 HISTORY AND BACKGROUND

- **1990** Exendin-4 discovered in Gila monster venom by John Eng; showed insulinotropic and glucose-lowering effects.
- **2005** Exenatide became the first incretin analogue approved for type 2 diabetes.
- **2000s–2010s** Pharmaceutical innovation extended half-life, improved efficacy and safety of GLP-1 receptor agonists.
- **2010s–2020s** Expansion to dual (GLP-1/GIP) and triple (GLP-1/GIP/Glucagon) agonists and oral non-peptide formulations.



The incretin revolution has transformed care for diabetes, obesity and multiple comorbidities.

2 PHYSIOLOGY & MECHANISM OF ACTION



GLP-1 RECEPTOR AGONISTS ACT ON MULTIPLE ORGANS

PANCREAS
- ↑ Glucose-dependent insulin secretion
- ↓ Glucagon secretion
- ↑ β-cell survival & proliferation

GASTROINTESTINAL TRACT
- ↓ Gastric emptying
- ↑ Satiety → reduced food intake

BRAIN (CNS)
Act on hypothalamus, nucleus accumbens, ventral tegmental area & vagus nerve
- ↓ Appetite, food reward & inflammation

CARDIOVASCULAR SYSTEM
- ↓ Blood pressure, ↓ inflammation,
- ↑ Endothelial function

KIDNEY
- ↑ Natriuresis, ↓ albuminuria, renal protection

Net Effect: Improved glycaemic control • Weight loss • Organ protection

3 CURRENT APPROVED GLP-1–BASED THERAPIES (2026)

	AGENT	CLASS / ACTION	DOSING	APPROVED USE
1	**Semaglutide** (Ozempic®, Wegovy®), Rybelsus®)	GLP-1 RA	Weekly SC or Daily Oral	• T2DM • Obesity (Wegovy®)
2	**Liraglutide** (Victoza®, Saxenda®)	GLP-1 RA	Daily SC	• T2DM • Obesity (Saxenda®)
3	**Tirzepatide** (Mounjaro®)	Dual GIP / GLP-1 RA	Weekly SC	• T2DM • Obesity
4	**Dulaglutide** (Trulicity®)	GLP-1 RA	Weekly SC	• T2DM
5	**Exenatide** (Byetta®, Bydureon®)	GLP-1 RA	BID SC or Weekly SC	• T2DM
6	**Lixisenatide** (Adlyxin®)	GLP-1 RA	Daily SC	• T2DM
7	**Beinaglutide** (Research)	GLP-1 RA	Periodic SC	• T2DM • Obesity (investigational)

RA: Receptor Agonist; SC: Subcutaneous, BID: Twice Daily; T2DM: Type 2 Diabetes Mellitus

4 EMERGING & EXPERIMENTAL THERAPIES IN DEVELOPMENT

TRIPLE & DUAL AGONISTS
- **Retatrutide** (GLP-1/GIP/Glucagon)
- **Cagrilintide–Semaglutide** (GLP-1/Amylin)
- **VK2735** (GLP-1/GIP) – injectable/oral
- **Survodutide** (GLP-1/Glucagon)
- **Amycretin** (GLP-1/Amylin)

GLP-1 / GLUCAGON COMBINATIONS
- **Mazdutide** (GLP-1/Glucagon mimic)
- **Maridebart cafraglutide** (GLP-1 RA with GIP receptor blockade)

ORAL NON-PEPTIDE GLP-1 AGONISTS
- **Orforglipron** (Phase 3)
- **Danuglipron** (Phase 2)
- **GSBR-1290** (Phase 2)
- **Ecnoglutide** (XW003) (Weekly SC)

NOVEL MECHANISMS
- **ARD-101** (Bitter-taste receptor agonist)
- **APHD-012** (Jejunal-release dextrose bead)
- **Monlunabant** (CB1 inverse agonist)
- **Bimagrumab** (Activin receptor antibody)

Goal: Greater efficacy, convenience, multi-targeted metabolic benefits and broader patient access.

5 BROAD CLINICAL BENEFITS OF GLP-1 RECEPTOR AGONISTS

GLYCAEMIC CONTROL & METABOLIC BENEFITS
- ↓ HbA1c by 1.5–2.0%+
- Glucose-dependent action (low hypoglycaemia risk)
- ↓ Post-prandial glucagon
- ↑ β-cell function & survival
- Improve NAFLD/NASH (histological benefits)

WEIGHT MANAGEMENT & BODY COMPOSITION
- 15–21% body weight loss (tirzepatide)
- Preferential fat mass loss, including visceral fat
- Preserves lean mass
- Improves SMM/VAT ratio
- Enhances metabolic health

CARDIOVASCULAR BENEFITS
- ↓ Major Adverse CV Events (26% in SUSTAIN 6; 14% in SOUL)
- ↓ Blood pressure
- ↑ Endothelial function
- ↓ Systemic inflammation

RENAL PROTECTION
- ↓ New or worsening nephropathy (36% in SUSTAIN 6)
- Macroalbuminuria –50%
- Slows progression to kidney failure

EXTRA-METABOLIC BENEFITS
- ↓ COPD, pneumonia & respiratory failure risk
- ↓ Sepsis & COVID-19 mortality
- ↓ Neurocognitive decline, Alzheimer's disease & dementia (observational)
- ↓ Risk of addictions (alcohol, cannabis, opioid)
- ↓ Seizures, psychosis & suicidal ideation (observational)

OVERALL IMPACT

GLP-1 RAs are transforming care across metabolic and non-metabolic diseases with proven and emerging multisystem benefits.

6 ADVERSE EFFECTS & SAFETY CONSIDERATIONS

GASTROINTESTINAL (Most Common)
- Nausea, vomiting
- Diarrhoea, constipation
- Abdominal pain
- Dyspepsia, bloating
- GERD, gastritis
- Gastroparesis, bowel obstruction

PANCREATIC & BILIARY
- ↑ Risk of acute pancreatitis
- ↑ Gallstones, cholecystitis, cholangitis (1.5×)

RENAL
- AKI (prerenal) from GI losses
- Acute interstitial nephritis, ATN
- ↑ Risk of kidney stones

OCULAR
- Worsening diabetic retinopathy
- Associated with rapid HbA1c reduction (especially first 16 weeks)

MUSCULOSKELETAL & BODY COMPOSITION
- Reduction in lean mass
- ↓ Bone mineral density (–1% at 1 year)
- Arthralgia, arthritis, tendinitis)

HYPERSENSITIVITY & DERMATOLOGIC
- Injection site reactions
- Anaphylaxis (rare)
- "Ozempic face" (facial fat loss)
- Alopecia, bullous pemphigoid (rare)

METABOLIC & SYSTEMIC
- Hypoglycaemia with insulin/sulfonylureas
- DKA with rapid insulin reduction
- Hypotension, syncope
- Fatigue, headache, dizziness

RISKS OF COMPOUNDED / UNREGULATED PRODUCTS: Dosing errors (up to 10×), contamination, non-sterile preparation, and lack of quality control may lead to severe GI events, infections (e.g., fungal meningitis), and unpredictable outcomes.

7 COMPARISON WITH OTHER THERAPIES

THERAPY	GLYCAEMIC EFFICACY	WEIGHT EFFECT	CV BENEFIT	RENAL BENEFIT	HYPOGLYCAEMIA RISK
Metformin	Moderate	Neutral / slight loss	Neutral	Some benefit	Low
GLP-1 RAs	High	Significant loss	Yes (established)	Yes (established)	Low
SGLT2 Inhibitors	Moderate	Modest loss	Yes (established)	Yes (strong)	Low
Insulin	High	Gain	Neutral	Neutral	High

GLP-1 RAs complement other agents; combination strategies optimize patient outcomes.

8 FUTURE DIRECTIONS

Expand Indications
Investigate in obesity, NASH, HFpEF, CKD, neurodegenerative disease, addictions, psychiatric disorders (investigational).

Next-Generation Therapies
Oral non-peptide agents, multi-agonists, biased agonism, tissue-specific delivery.

Personalised Medicine
Tailor therapy by genetics, sex, phenotype & comorbidities for maximal benefit.

Equity & Access
Ensure affordability and access for underrepresented populations.

Safety & Regulation
Strengthen oversight of compounded products and long-term safety monitoring.

9 CONCLUSION

GLP-1 receptor agonists have evolved from targeted antihyperglycaemic drugs to cornerstone multisystem therapeutics. They deliver powerful metabolic benefits with proven cardiovascular and renal protection, and emerging advantages in brain health and inflammation.

Although adverse effects require careful monitoring, continued innovation promises oral agents, multi-pathway therapies and greater patient access.

In 2026, GLP-1–based therapies represent a paradigm shift in chronic disease management.

GLP-1 RAs: Comprehensive care. Multi-organ protection. Transforming lives.

Key trials: DURATION • LEAD • SUSTAIN • STEP • SURMOUNT • SOUL