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## Review Article

# Beyond glycemic control: emerging therapeutic applications of GLP-1 receptor agonists: a comprehensive narrative review

Nidhi Srivastava\*, Siddhant Mehrotra, Shubham Biswas, Ayush Jain, Rakesh Kumar Dixit

Department of Pharmacology, King George's Medical University, Lucknow, Uttar Pradesh, India

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### \*Correspondence:

Dr. Nidhi Srivastava,

Email: [drnidhisrivastavakgm@gmail.com](mailto:drnidhisrivastavakgm@gmail.com)

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## ABSTRACT

The therapy of type 2 diabetes mellitus and obesity has been changed by glucagon-like peptide-1 receptor agonists (GLP-1 RAs). However, clinical evidences suggest their therapeutic potential extends far beyond glycaemic management with major function in cardiovascular, hepatic, renal and neurological illnesses To give a complete appraisal of the emerging non-glycaemic therapeutic potential of GLP-1 RAs through a survey of the available clinical evidence and to highlight future research options in this rapidly growing field. A thorough literature search was performed in the PubMed, Scopus and Google Scholar databases from inception to November 2025. The search criteria included GLP-1 receptor agonists, semaglutide, tirzepatide, and combinations with specified therapeutic areas. Clinical trials, systematic reviews and mechanistic research of landmark importance were prioritized GLP-1 RAs have shown important cardiovascular benefits, decreasing major adverse cardiovascular events (MACE) by 20%. Tirzepatide reduced heart failure hospitalization by 38% in patients with heart failure with intact ejection fraction. These medicines show potential for decreasing hepatic steatosis and fibrosis in metabolic dysfunction-associated steatotic liver disease . Observational studies demonstrate a 48% reduction in incidence of dementia and growing evidence suggests neuroprotective effects. Other therapeutic uses are for chronic renal disease, polycystic ovary syndrome, obstructive sleep apnoea and substance use disorders. GLP-1 RAs represent a paradigm change in pharmacology, evolving from glucose-lowering to multi-organ protecting treatments. The development of multiple and triple agonists and oral non-peptide formulations will certainly greatly enhance their clinical value.

**Keywords:** GLP-1 receptor agonists, Semaglutide, Tirzepatide, Cardiovascular protection, MASLD, Neuroprotection, Obesity, Pleiotropic effects

## INTRODUCTION

The discovery of the incretin effect in the 1960s was the foundation for one of the most important advances in the pharmacology of metabolic medicine. Glucagon-like peptide-1 (GLP-1) was identified as a 30-amino acid peptide hormone secreted by intestinal L-cells following food ingestion and as a critical modulator of glucose-dependent insulin secretion. The emergence of GLP-1

receptor agonists (GLP-1 RAs) has changed the therapeutic approach to type 2 diabetes mellitus (T2DM) and is being used in a broad spectrum of metabolic and non-metabolic diseases.

The first GLP-1 RA, exenatide, was approved by the FDA in 2005, representing a paradigm shift in diabetes management. The class has come a long way since then, from twice daily injections to once weekly formulations

and most recently oral preparations. The approval of Semaglutide for chronic weight management in 2021 and the subsequent introduction of Tirzepatide, a dual GLP-1/glucose-dependent insulintropic polypeptide (GIP) receptor agonist, have significantly enlarged the therapeutic possibilities of incretin-based medicines.

The GLP-1 receptor is expressed in pancreatic beta cells as well as in extra-pancreatic tissues such as the heart, blood vessels, kidneys, liver and brain. The wide distribution of the receptor explains the pleiotropic effects of GLP-1 RAs, which go beyond the usual glycemic control.<sup>1,2</sup> Clinical data showing cardiovascular benefits in diabetes trials, mechanistic studies showing anti-inflammatory, anti-atherosclerotic and neuroprotective effects have generated a lot of scientific interest in non-glycaemic applications.

This narrative review considers the wider therapeutic utility of GLP-1 receptor agonists beyond glycaemic control and describes the latest evidence for their role in cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), neurodegenerative disorders, chronic kidney disease, polycystic ovary syndrome, obstructive sleep apnoea and substance use disorders. Key safety considerations and future perspectives are also discussed, including the development of next-generation incretin-based medicines that are likely to further transform this therapy class.

## CLASSIFICATION AND MECHANISM OF ACTION

### *Classification of GLP-1 based therapies*

According to the structural backbone, GLP-1 receptor agonists can be divided into exendin-4-based and human GLP-1-based medicines. Exendin-4-based agonists, such as exenatide and lixisenatide, are synthesized from a peptide in the saliva of the Gila monster that has ~53% sequence homology to endogenous human GLP-1. Human GLP-1-based medicines such as liraglutide, semaglutide and dulaglutide are modified copies of endogenous GLP-1 engineered to withstand dipeptidyl peptidase-4 (DPP-4) breakdown by precise amino acid substitution and fatty acid acylation.<sup>1,2</sup>

More recently, the therapeutic landscape has extended to include multi-agonist therapies. Tirzepatide is a dual GIP/GLP-1 receptor agonist approved in 2022, which targets both incretin pathways and shows greater reduction in glycaemic and weight than selective GLP-1 Ras.<sup>3</sup> Of particular interest, triple agonists such as retatrutide, which simultaneously target GLP-1, GIP, and glucagon receptors, have exhibited exceptional weight reduction of up to 24% in phase II clinical trials.<sup>4</sup>

**Table 1: Classification of GLP-1 based therapies.**

| Agent               | Class             | Administration      | Half-life   | Year approved |
|---------------------|-------------------|---------------------|-------------|---------------|
| <b>Exenatide</b>    | Exendin-4 based   | Twice daily SC      | 2.4 hours   | 2005          |
| <b>Liraglutide</b>  | Human GLP-1 based | Once daily SC       | 13 hours    | 2010          |
| <b>Dulaglutide</b>  | Human GLP-1 based | Once weekly SC      | 5 days      | 2014          |
| <b>Semaglutide</b>  | Human GLP-1 based | Once weekly SC/Oral | 7 days      | 2017          |
| <b>Tirzepatide</b>  | Dual GIP/GLP-1    | Once weekly SC      | 5 days      | 2022          |
| <b>Retatrutide</b>  | Triple agonist    | Once weekly SC      | 6 days      | Phase 3       |
| <b>Orforglipron</b> | Non-peptide GLP-1 | Once daily Oral     | 29-49 hours | Phase 3       |

SC: Subcutaneous; GIP: Glucose-dependent insulintropic polypeptide

### *Mechanisms of Action*

The main mechanism of GLP-1 RAs is the activation of the GLP-1 receptor, a G-protein coupled receptor that stimulates adenylyl cyclase and increases intracellular cyclic AMP.

In pancreatic beta cells this leads to glucose-dependent insulin production, beta-cell proliferation and decreased apoptosis. In addition, GLP-1 RAs block glucagon release from alpha cells in a glucose dependent manner, which helps to enhance glycaemic control.

In addition to pancreatic actions, GLP-1 RAs have important central nervous system effects through receptors in the hypothalamus and brainstem that reduce hunger and promote satiety. This central mechanism, along with delayed stomach emptying, accounts for the substantial weight loss seen with these drugs.

The cardiovascular benefits appear to be transmitted through several routes including anti-inflammatory effects, improvement of endothelial function, reduction in atherogenic lipoproteins and direct cardioprotective signalling.

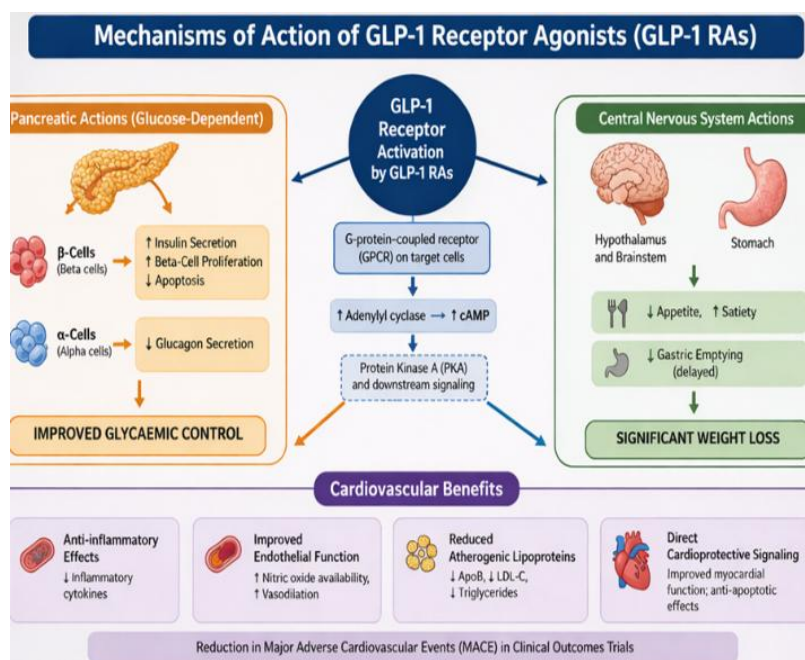


**Figure 1: Mechanisms of action.**

## EMERGING THERAPEUTIC APPLICATIONS

### Cardiovascular protection

A series of large cardiovascular outcome trials have established the cardiovascular advantages of GLP-1 RAs. The LEADER study revealed that liraglutide reduced the risk of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke by 13% compared to placebo in individuals with T2DM at high cardiovascular risk. Then, the SUSTAIN-6 study revealed a 26% reduction in major adverse cardiovascular events (MACE) with semaglutide. These findings were extended to patients with obesity but without diabetes in the landmark SELECT trial, published in 2023. In a landmark study, semaglutide 2.4 mg weekly lowered MACE by 20% compared to placebo, demonstrating for the first time that the cardiovascular effects of GLP-1 RAs are independent of glucose reduction. The experiment randomized more than 17,000 patients with known cardiovascular disease and a body mass index of 27 kg/m<sup>2</sup> or higher and followed them for an average of 40 months.<sup>5</sup> The SUMMIT trial studied tirzepatide in individuals with obesity and heart failure with preserved ejection fraction (HFpEF). Tirzepatide lowered the risk of cardiovascular mortality or worsening heart failure events by 38%. These results are particularly striking, because tirzepatide is the first pharmacologic agent that has demonstrated prognostic improvement in HFpEF, a disease for which there have been no effective therapeutic choices for a long time.<sup>6</sup>

The cardiovascular benefits of GLP-1 receptor agonists seem to go beyond their effects on body weight and

glycaemic management. The proposed mechanisms include attenuation of systemic inflammation, reduction of oxidized low-density lipoprotein cholesterol, enhancement of endothelial function, and direct anti-atherosclerotic activities within the arterial wall. Preclinical investigations have also revealed a reduction in infarct size in cardiac ischaemia-reperfusion injury, suggesting the presence of direct cardioprotective signalling pathways.

### Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) (formerly called non-alcoholic fatty liver disease [NAFLD]) affects roughly 25% of the world's population and is a leading cause of chronic liver disease. Pathophysiology includes hepatic fat buildup, inflammation and progressive fibrosis with insulin resistance being a significant factor. GLP-1 receptor agonists exert pleiotropic effects on various pathological pathways and are therefore interesting therapeutic agents beyond glycaemic control. The LEAN trial was the first randomized controlled study to assess liraglutide in patients with biopsy-proven non-alcoholic steatohepatitis (NASH). 39% of patients treated with liraglutide had histological clearance of NASH at 48 weeks compared with 9% of individuals treated with placebo. Furthermore, there was no deterioration of fibrosis in the liraglutide group.<sup>7</sup> More recent imaging investigations with semaglutide have showed substantial decreases in liver fat content, frequently more than 30% from baseline.<sup>8</sup>

Tirzepatide had very promising outcomes in MASLD. The SYNERGY-NASH trial investigated tirzepatide in patients with biopsy-confirmed NASH and revealed that as

many as 74% of people at the highest dose had their NASH cured without the progression of fibrosis. In addition, a considerable majority of patients demonstrated at least one-stage improvement in fibrosis, suggesting that these medicines could have disease-modifying effects beyond the reduction of hepatic steatosis.<sup>8</sup> GLP-1 RAs possess hepatoprotective mechanisms that directly affect the lipid metabolism of hepatocytes, reducing de novo lipogenesis, increasing fatty acid oxidation, and diminishing hepatic inflammation. Weight loss appears to be a key factor in these benefits, although analyses that account for changes in body weight indicate that GLP-1 receptor agonists may also exert direct hepatic effects irrespective of weight loss. Modulation of the gut–liver axis has been suggested as another pathway, which may be mediated by beneficial changes in the intestinal microbiome that result in hepatic health.

### ***Neurodegenerative diseases***

The discovery of GLP-1 receptors in the central nervous system, in particular, in the hippocampus and cortex, has stimulated research into the use of GLP-1 RAs in neurodegenerative illnesses. Evidence from pre-clinical trials shows that GLP-1 RAs have neuroprotective effects by lowering neuroinflammation, boosting synaptic plasticity, reducing amyloid-beta deposition and improving mitochondrial function. The results have garnered considerable attention in the areas of Alzheimer's disease and Parkinson's disease.

The EXENATIDE-PD trial was the first clinical indication of possible neuroprotection in Parkinson's disease. After 48 weeks, motor scores increased by 3.5 points in the exenatide treated patients compared to a 2.1-point decrease in the placebo group. Remarkably, this effect was still present at the 12-week follow-up after drug washout, raising the possibility of disease modification rather than clinical improvement alone.<sup>9</sup> There is a body of evidence from large observational studies that supports the rationale for neuroprotection. A cohort study of almost 100,000 patients at the University of Oxford showed that GLP-1 RA users had a 48% lower chance of acquiring dementia than non-users after adjusting for several variables, including the duration of diabetes and glycaemic management. Similar results have been reported in Scandinavian registry studies.<sup>9</sup> Several randomized controlled trials are presently underway to investigate the use of GLP-1 RAs in Alzheimer's disease and Parkinson's disease. The EVOKE trial is studying semaglutide in early Alzheimer's, whereas the Liraglutide-PD trial is studying disease progression in Parkinson's. Results from these trials are much awaited and could provide a new therapeutic paradigm for neurodegenerative diseases.

### ***Chronic kidney disease***

GLP-1 receptors are expressed in the kidney and GLP-1 RAs have showed renoprotective effects via a number of pathways including natriuresis, reduction in glomerular

hyperfiltration, anti-inflammatory effects and lowered oxidative stress. Post-hoc analysis of cardiovascular outcome trials regularly shown decreases in the course of albuminuria, resulting in dedicated renal outcome investigations.

The FLOW trial, published in 2024, was the first renal outcomes trial dedicated to a GLP-1 RA. Semaglutide 1.0 mg weekly reduced the composite kidney outcome (sustained 50% decline in eGFR, kidney failure or kidney death) by 24% compared to placebo in patients with T2DM and chronic kidney disease. The experiment was discontinued early because of overwhelming efficacy and notably cardiovascular death was also reduced by 28%.<sup>10</sup>

These findings place GLP-1 RAs as crucial additions to the Reno protective armamentarium together with SGLT2 inhibitors and finerenone. Whether there are additive or synergistic advantages with combination therapy yet to be determined. Current guidelines promote GLP-1 RAs as preferred treatments in patients with T2DM and chronic renal disease, especially when cardiovascular risk is high.

### ***Polycystic ovary syndrome***

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting 6-12% of women of reproductive age and characterized by hyperandrogenism, ovulatory dysfunction, and metabolic abnormalities including insulin resistance and obesity. The fundamental involvement of insulin resistance in PCOS pathogenesis provides a basis for GLP-1 RA treatment that targets both metabolic and reproductive symptoms.

Clinical studies have shown that GLP-1 RAs markedly ameliorate PCOS. Exenatide and liraglutide have been proven to lower body weight, increase insulin sensitivity, decrease testosterone levels, and restore menstrual regularity in women with PCOS. Although some studies have indicated improved ovulation rates and pregnancy outcomes, larger studies aimed to determine fertility endpoints are needed. The combination of GLP-1 RAs and metformin appears to be particularly effective, leading to higher improvements in metabolic and reproductive parameters than either drug alone. Tirzepatide's dual agonist action may offer further benefits, however clinical data in PCOS populations are still emerging. The weight loss achieved with GLP-1 RAs is of particular interest given that even a little reduction in weight (5–10%) might lead to substantial improvement in PCOS symptoms

### ***Obstructive sleep apnea***

Obesity is the most important modifiable risk factor for obstructive sleep apnoea (OSA) and weight reduction has been associated with improvement of apnoea hypopnoea index (AHI) and other sleep metrics. The impressive weight loss obtained with GLP-1 RAs has spurred devoted inquiry in OSA populations.

The SURMOUNT-OSA trials assessed tirzepatide in individuals with moderate-to-severe OSA and obesity. The results showed a significant reduction of roughly 50-60% in AHI, which was greater than the benefits obtained with lifestyle modification alone. In 2024, the FDA approved tirzepatide for the treatment of moderate-to-severe OSA in people with obesity, the first pharmaceutical medication for this indication. In addition to weight loss, potential pathways by which GLP-1 RAs can treat OSA include reduced fluid retention, decreased pharyngeal fat deposition, and putative effects on central respiratory control. The link between GLP-1 RAs and OSA is particularly relevant because of the reciprocal relationship between sleep apnoea and metabolic dysregulation.

### Substance use disorders

An interesting emerging application of GLP-1 RAs is in substance use disorders. The GLP-1 receptor is expressed in brain areas involved in reward processing including the

ventral tegmental area and nucleus accumbens. GLP-1 RAs have been found in animal models to reduce alcohol consumption, cocaine self-administration and nicotine-seeking behaviour in pre-clinical investigations.

Observational studies in humans have provided supporting evidence. Analysis of major healthcare datasets has shown that individuals prescribed GLP-1 RAs for diabetes or obesity have lower rates of alcohol use disorder diagnoses and fewer opioid prescriptions than matched controls. Patients anecdotal reports decreased urges for alcohol and food at the same time. Randomized controlled trials are being conducted to properly test GLP-1 RAs in addiction. Studies are looking at semaglutide and other drugs in alcohol use disorder, opioid use disorder, and smoking cessation. If favorable, these findings could considerably increase the therapeutic impact of this pharmacological class to tackle key public health concerns outside metabolic disorder.

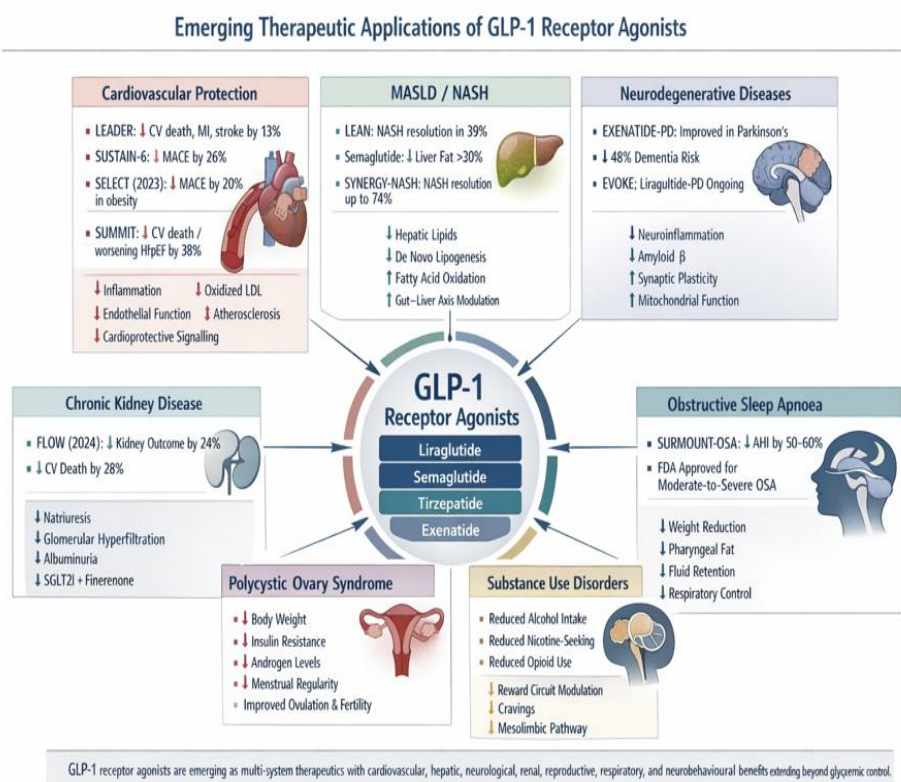


**Figure 2: GLP-1 Receptor agonist.**

### Safety considerations

Generally, GLP-1 RAs are well tolerated with gastrointestinal adverse effects being the most common.

Nausea, vomiting and diarrhea occur in 20-50% of patients, often during dose increase and normally improve with sustained medication. These effects can be minimized by slow titration of the dose. Injection site responses reported but usually moderate.

**Table 2: Safety considerations with GLP-1 receptor agonists.**

| Adverse effect                             | Frequency/Evidence                    | Clinical recommendation                                          |
|--------------------------------------------|---------------------------------------|------------------------------------------------------------------|
| <b>Gastrointestinal (nausea, vomiting)</b> | 20-50%, dose-dependent                | Slow titration, take with meals initially                        |
| <b>Acute pancreatitis</b>                  | Rare, ~0.1-0.3%                       | Avoid in history of pancreatitis; discontinue if suspected       |
| <b>Gallbladder disease</b>                 | Increased risk with rapid weight loss | Monitor symptoms; consider prophylaxis with high weight loss     |
| <b>Thyroid C-cell tumours</b>              | Rodent signal; no human evidence      | Contraindicated in MTC/MEN2; monitor thyroid nodules             |
| <b>Hypoglycemia</b>                        | Low risk as monotherapy               | Caution with sulfonylureas/insulin; dose reduction may be needed |
| <b>Psychiatric effects</b>                 | Under investigation; conflicting data | Monitor mood changes; report suicidal ideation                   |

MTC: Medullary thyroid carcinoma; MEN2: Multiple endocrine neoplasia type 2

In fact, long-term safety data from cardiovascular outcome trials have not revealed higher risk of pancreatitis or pancreatic cancer, greatly allaying concerns. GLP-1 RAs remain contraindicated in people with a history of pancreatitis nevertheless. While rodent carcinogenicity studies raise a theoretical concern for medullary thyroid carcinoma, this has not been confirmed in human studies, however, these agents are contraindicated in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2.<sup>11,12</sup>

Gallbladder and biliary illness are a genuine safety warning with increased frequency of cholelithiasis and cholecystitis in clinical trials, likely due to rapid weight reduction. Delayed stomach emptying and perioperative aspiration risk have resulted in suggestions to hold GLP-1 RAs before to elective surgery, however the timing is controversial. Psychiatric safety, particularly suicidal ideation, has become an area of regulatory emphasis. European regulators started a review based on spontaneous reports while further reviews of clinical trial data have not found higher psychiatric side events. Ongoing pharmacovigilance surveillance is continuing and doctors should be alerted to mood changes in patients who start medication.

Re-gain of weight after cessation is a serious clinical concern. Extension trial data reveal that individuals recover around 67% of their lost weight within 1 year of discontinuing medication and cardiometabolic advantages are reversed.<sup>13</sup> This underscores the chronic, relapsing nature of obesity and the likely requirement for long-term medication in many patients.

## CONCLUSION

GLP-1 receptor agonists have transitioned from glucose-lowering medications to multi-organ protective treatments with implications for cardiovascular medicine, hepatology, nephrology, neurology, and beyond. The robust data for cardiovascular benefit including the paradigm-shifting SELECT trial demonstrating a reduction in MACE in non-

diabetic obesity, has revolutionized our knowledge of the therapeutic potential of these medications. The pipeline of next-generation incretin treatments, including dual and triple agonists, oral non-peptide formulations, and ultra-long-acting medicines, offers continuous innovation and broadening of clinical relevance. With increasing evidence for applications in neurodegenerative illnesses, substance use disorders and other problems, the therapeutic footprint of this class is anticipated to continue to rise.

Clinicians need to understand the opportunities and limitations of GLP-1 RAs. Generally well tolerated, careful patient selection, moderate dose increase and awareness for safety signals are necessary. The problem of weight regains after ceasing medication underlines the chronic nature of obesity and the need for long-term treatment in many people. The shift of GLP-1 RAs from diabetic drugs to core metabolic medicines is one of the most significant pharmaceutical breakthroughs of the 21st century. Future studies will further characterize the best patient populations, combinatorial strategies, and long-term outcomes to apply these potent therapeutic drugs in a precise manner.

## Future directions

The GLP-1 RA sector is evolving rapidly and there are many exciting advancements on the horizon. Weight reduction >24% has been observed in clinical trials with triple agonists of GLP-1, GIP and glucagon receptors such as retatrutide, approaching that attained with surgery. The glucagon receptor component may raise energy expenditure and hepatic fat oxidation, which may offer further metabolic benefits.

The oral non-peptide GLP-1 RAs could be a paradigm change in medication delivery. Phase 3 trials of Orforglipron, a small molecule GLP-1 RA, show good efficacy and may overcome hurdles to injectable delivery. Another oral contender in development is Danuglipron. These agents could significantly increase access and patient acceptance. Ultra-long-acting formulations are under development to decrease dose frequency. Early trials

have showed MariTide to be effective for a sustained period with approximately a 21-day half-life and the possibility for dosing intervals of a month or more. Such formulations may increase compliance and convenience.

Combination techniques are being increasingly investigated. Additive weight reduction benefits have been shown with the combination of semaglutide and cagrilintide, a long-acting amylin analogue. Also, combinations with investigational medicines targeting other mechanisms of energy homeostasis are under development. Precision medicine techniques may in the future allow for personalized selection of incretin medicines based on genetics, metabolism, or microbiota. Identification of patients who respond well to GLP-1 versus GIP versus glucagon receptor activation could allow for personalized therapy. The gut microbiome is becoming recognized to influence GLP-1 RA responsiveness and potentially serve as indicators for medication selection.

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