Drug Design, Development and Therapy

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REVIEW

The Clinical Application of GLP-1RAs and GLP-1/GIP Dual Receptor Agonists Based on Pharmacological Mechanisms: A Review

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Abstract: This review provides a comprehensive examination of the clinical pharmacological mechanisms and broad therapeutic applications of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual receptor agonists targeting both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. GLP-1RAs exert their effects by stimulating insulin secretion, suppressing glucagon release, delaying gastric emptying, and reducing appetite through the activation of the GLP-1 receptor. These agents have demonstrated significant efficacy in the management of type 2 diabetes mellitus (T2DM) and obesity. Moreover, emerging evidence suggests that GLP-1RAs may confer cardiovascular protection, neuroprotective benefits, and positive effects on mental health. Dual GLP-1/GIP receptor agonists, such as tirzepatide, simultaneously activate both receptors, thereby potentiating glycemic control, promoting weight loss, and ameliorating metabolic dysfunction. This review also addresses recent advances in the development of other dual and triple receptor agonists. Distinct from prior reviews that predominantly focus on a single drug class or limited clinical indications, this article systematically contrasts the mechanistic pathways, therapeutic efficacy, and safety profiles of GLP-1RAs versus GLP-1/GIP dual receptor agonists. Notably, it integrates the most current evidence pertaining to novel domains, such as perioperative management, neuropsychiatric outcomes, and the innovation of multi-receptor agonists. This synthesis offers a timely and practical resource to inform clinical precision medicine and to guide future investigative efforts.

Keywords: GLP-1RAs, GLP-1/GIP dual receptor agonist, tirzepatide, clinical pharmacology, T2DM, obesity, neuroprotection

Introduction

Glucagon-like peptide-1 (GLP-1) is a small-peptide hormone. It is synthesized by intestinal L cells and specific neuronal populations within the caudal medulla.[1] Owing to its diverse physiological functions, GLP-1 is a promising therapeutic target for diabetes and obesity management. Notably, GLP-1 exerts significant effects on glycemic control by promoting glucose-stimulated insulin secretion and suppressing glucagon release.[1–3] Additionally, it reduces appetite and food intake.[1,4,5] Glucagon-like peptide-1 receptor agonists (GLP-1RAs), which mimic the action of endogenous GLP-1, have become integral to the treatment of type 2 diabetes mellitus (T2DM). Current guidelines from Europe[6] and the United States[7] recommend initiating GLP-1RAs therapy promptly after the failure of oral hypoglycemic agents, prioritizing their use over insulin therapy.

Despite these advances, several clinical challenges remain to be overcome. In obesity management, conventional interventions, such as lifestyle modification and traditional pharmacotherapy, demonstrate limited efficacy in patients with moderate to severe obesity, and sustained weight loss is difficult to achieve. Moreover, optimal therapeutic strategies to concurrently address obesity-related cardiovascular and metabolic comorbidities, including hypertension and dyslipidemia, are lacking. Patients with T2DM and obesity exhibit an elevated risk of adverse cardiovascular events. Although conventional hypoglycemic agents effectively control blood glucose levels, they inadequately prevent major adverse cardiovascular events, such as myocardial infarction and stroke. This is particularly evident in specific cardiovascular

Received: 11 August 2025
Accepted: 15 November 2025
Published: 22 November 2025

conditions such as heart failure with preserved ejection fraction (HFpEF), for which effective treatments are scarce. Furthermore, in the domain of neurodegenerative diseases, individuals with T2DM have a markedly increased risk of Alzheimer's and Parkinson's disease. Existing therapeutic options fail to halt neurodegeneration by modulating metabolic dysfunction, leaving the neuroprotective clinical needs largely unmet.

Several strategies have been explored to enhance the therapeutic efficacy of GLP-1RAs, several strategies have been explored.[8] Dose escalation has been employed, although adverse gastrointestinal effects may limit tolerability. Higher doses of dulaglutide[9] and semaglutide[10] have demonstrated improved weight reduction and glycemic control in T2DM patients. Among emerging approaches, the development of dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists represents a particularly innovative and promising paradigm.[11] These novel agents offer new avenues for the treatment of T2DM and obesity.[12,13]

Although GLP-1RAs confer substantial clinical benefits, safety considerations persist. The cardiovascular safety profiles of GLP-1RAs are favorable, with no significant increase in the incidence of acute pancreatitis or pancreatic cancer reported.[14] However, their use is associated with a higher frequency of gastrointestinal adverse events, such as nausea, vomiting, and diarrhea.[15] GLP-1RAs are considered safe in patients with chronic kidney disease and effective in reducing the risk of severe hypoglycemia.[16] In individuals with established cardiovascular diseases, GLP-1RAs have been shown to significantly lower the risk of major adverse cardiovascular events.[15] Nevertheless, limited cardiovascular and renal outcome data for certain agents, such as oral semaglutide, have constrained their broader clinical application.[17] In the context of post-transplant diabetes, GLP-1RAs exhibit efficacy and safety profiles comparable to those observed in non-transplant populations.[18]

This review was conducted through comprehensive searches of electronic databases, including Web of Science and PubMed, using a full-text search strategy. Search terms included "glucagon-like peptide-1 receptor agonist", "GLP-1 receptor agonists", "GLP-1RAs", "GLP-1/GIP dual receptor agonists", "exenatide", "liraglutide", "dulaglutide", "albiglutide", "lixisenatide", "semaglutide", and "tirzepatide", combined using Boolean operators "OR" and "AND." Given the broad scope of this review, disease-specific terms were excluded. The literature search included publications up to July 1, 2025.

This manuscript provides a comprehensive summary of the clinical pharmacology of GLP-1RAs and GLP-1/GIP dual receptor agonists, with particular emphasis on tirzepatide.[19] The objective was to comprehensively review their pharmacological properties and clinical applications, thereby supporting precision medicine and rational pharmacotherapy within the authors' clinical setting. Additionally, this review serves as an educational resource for departmental teaching activities and offers guidance for future research within the team.

Distribution and Regulation of GLP-1 System

Although a deficiency in GLP-1 is unlikely to directly impair the pathophysiology of T2DM,[20] reduced GLP-1 levels may contribute to the development of T2DM.[21] Additionally, weight gain may reflect dysregulation of the GLP-1 system, thereby perpetuating metabolic dysfunction.[22] GLP-1 secretion plays a critical role in regulating various homeostatic mechanisms,[3,20] some of which overlap between peripheral and central GLP-1 systems. The incretin effect of GLP-1 leads to a marked postprandial increase in circulating levels, which enhances insulin secretion.[23,24] Elevated postprandial GLP-1 concentrations may be influenced by mechanical stimuli such as gastric distension,[3,25] which also activates GLP-1-expressing neurons in the nucleus tractus solitarius (NTS).[26] These responses may involve oxytocin-mediated vagal afferent signaling and contribute to the central GLP-1 system's role in promoting a negative energy balance.[27,28] Beyond mechanical stimuli, classical satiety hormones, such as cholecystokinin, augment both central GLP-1 neuronal activity and peripheral GLP-1 release;[29] however, the concentrations of cholecystokinin required to stimulate peripheral GLP-1 secretion may exceed physiological levels.[30] GLP-1 secretion is modulated by various peptides, neurotransmitters, and nutrients, including carbohydrates, lipids, proteins, and amino acids, highlighting the complexity of its regulatory mechanisms.[3,31]

GLP-1 exerts its effects via the G-protein-coupled receptor,[32,33] which is expressed on pancreatic beta cells as well as neurons within the central and peripheral nervous systems. The distinct expression patterns suggest nuanced and potentially non-redundant roles for GLP-1 signaling in these systems.[27] Activation of GLP-1 neurons in the NTS has

been shown to reduce metabolic rates and suppress food intake in both fed and fasted murine models.[2,28,34] Moreover, stimulation of NTS GLP-1 neurons inhibits hepatic glucose production without altering peripheral glucose uptake, illustrating the involvement of the central GLP-1 system in energy homeostasis and glucose metabolism.[34,35]

The hypothalamus serves as a principal downstream target for peripherally administered GLP-1RAs and GLP-1 neurons originating in the hindbrain.[36] Pharmacological studies in whole-animal models have demonstrated that the activation of GLP-1 receptors enhances glucose tolerance and suppresses food intake, thereby facilitating weight loss and improving glucose homeostasis.[37,38] Genetic approaches in mice further corroborate the physiological significance of GLP-1 receptor in the regulation of energy balance and glucose metabolism. Global GLP-1 receptor deficiency consistently results in attenuated glucose excursions during oral glucose tolerance tests, accompanied by reduced circulating insulin levels.[39] Conversely, GLP-1 receptor knockout mice exhibited elevated blood glucose levels in intraperitoneal glucose tolerance tests,[40] indicating that GLP-1 receptor is essential for maintaining normoglycemia. Systemic GLP-1 receptor deficiency impairs GLP-1-induced anorexia as anticipated.[41] However, these mice do not display alterations in baseline body weight, suggesting that GLP-1 receptor is not critical for body weight regulation under basal conditions.[41] Notably, subsequent investigations revealed that both male and female mice lacking systemic GLP-1 receptor are resistant to diet-induced obesity.[39,42]

Focusing on central mechanisms, intracerebroventricular administration of GLP-1 failed to modulate feeding behavior in GLP-1 receptor global knockout mice.[41] Central inhibition of GLP-1 receptor disrupts glucose homeostasis and reduces food intake, whereas peripheral GLP-1 receptor inactivation impairs glucose-stimulated insulin secretion, diminishes glucose clearance, elevates glucagon levels, and accelerates gastric emptying. However, these peripheral effects do not translate into increased food intake or body weight within 24 h following GLP-1 receptor blockade.[43,44] Collectively, these findings support the notion that brain GLP-1 receptors regulate feeding behavior and body weight,[3,20,24] complementing the limited phagocytosis of endogenous GLP-1 via peripheral receptors.[45] Given the rapid degradation of endogenous GLP-1 upon entering circulation, hypothalamic GLP-1 receptors are likely predominantly activated by GLP-1 neurons originating in the NTS.[32] Importantly, recently developed long-acting GLP-1 analogs have been demonstrated to target multiple brain nuclei, including the hypothalamus, thereby expanding the therapeutic potential of GLP-1-based interventions[36,46] (See Figure 1).

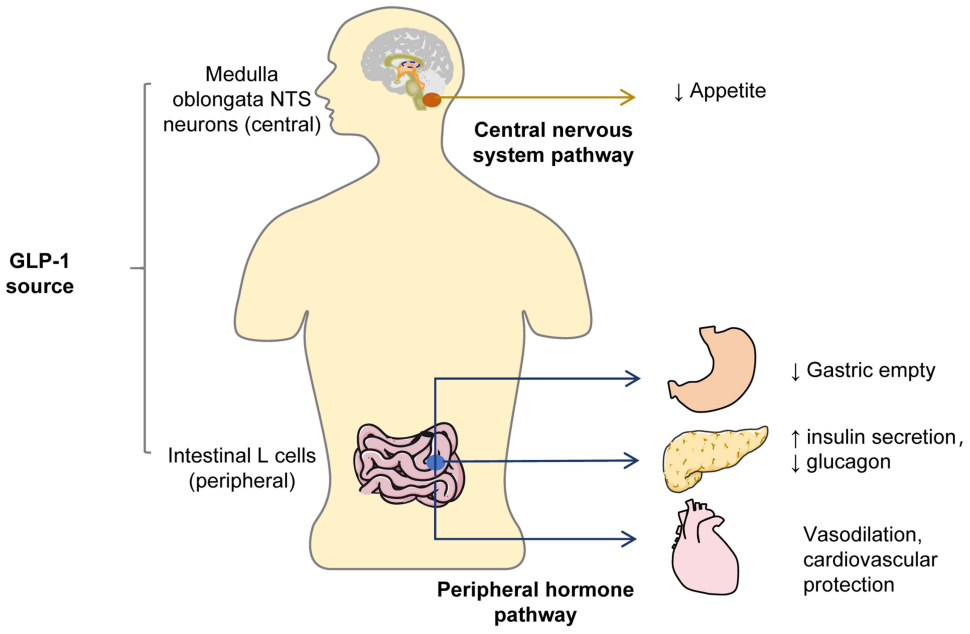

Figure 1 Central and peripheral effects of GLP-1 system. ↑: improve; ↓: decrease.

https://doi.org/10.2147/DDDT.S559919

Complementarity of GIP and GLP-1

GIP is an incretin hormone that enhances insulin secretion in response to nutrient ingestion.[47,48] Its influence on glucagon secretion is more intricate than that of GLP-1 and GLP-1RAs, which are established inhibitors of glucagon release. In normoglycemic and hyperglycemic conditions, the administration of GIP in healthy individuals suppresses glucagon secretion; however, under hypoglycemic conditions, GIP paradoxically stimulates the release of counterregulatory hormones.[13] Notably, these glucose-dependent modulatory effects on glucagon secretion appear to be diminished or absent in individuals with T2DM.[49] GIP reduces appetite and enhances satiety, thereby facilitating weight loss, although the precise mechanisms remain debated, with uncertainty as to whether these effects are direct or mediated indirectly through potentiation of GLP-1's anorectic actions.[13,48] Peripherally, GIP exerts beneficial effects on adipose tissue and skeletal muscle by promoting lipid storage in white adipose tissue and decreasing ectopic fat accumulation within the muscle, both of which contribute to improved insulin sensitivity.

Consequently, GIP and GLP-1 receptor agonists exhibit complementary and potentially synergistic actions, suggesting that their combined administration may further enhance glucose regulation and support weight reduction.[11–13,50] This rationale underpins the development of dual GLP-1/GIP receptor agonists, which have been proposed as "super-GLP-1 receptor agonists" because of GIP's capacity of GIP to potentiate GLP-1 effects.[48,51]

Clinical Pharmacology of GLP-1RAs

The "incretin effect" of GLP-1RAs was initially characterized by the observation that oral glucose administration elicits a proportionally greater and more sustained insulin secretion compared to an equivalent intravenous glucose dose.[52,53] This incretin effect, which accounts for approximately two-thirds of the total insulin secretion during an oral glucose tolerance test, is diminished in individuals with T2DM. GLP-1, a cleavage product of preproglucagon,[54,55] is secreted by L cells located in the terminal ileum and proximal colon in response to glucose and triglyceride stimulation. GLP-1 is also produced by pancreatic islet cells and neurons within the NTS of the brainstem.[56] The peptide is rapidly degraded by dipeptidyl peptidase-4 into GLP-1 amide and subsequently cleared renally, resulting in a short half-life of approximately two minutes.[47]

Activation of the G protein-coupled GLP-1 receptor increases intracellular calcium concentrations within pancreatic islets, thereby promoting insulin exocytosis. In the alpha cells of the islets, GLP-1 receptor activation suppresses glucagon secretion, a process mediated by somatostatin release from adjacent delta cells.[54,57] Beyond the pancreas, GLP-1 receptors are widely expressed in extrapancreatic tissues, including the heart, vascular smooth muscle, lungs, liver, gastrointestinal tract, vagus nerve, and enteric nervous system.[58]

GLP-1 receptor agonists exhibit varying degrees of homology with endogenous GLP-1 but possess extended durations of action. These agents are extensively utilized in managing T2DM and obesity and have demonstrated efficacy in reducing nonfatal myocardial infarction, stroke, and mortality in affected patients.[57,59] Exenatide, a synthetic peptide with 50% sequence homology to GLP-1, is resistant to dipeptidyl peptidase-4-mediated degradation[54] and was the first GLP-1RAs approved by the US Food and Drug Administration (FDA) for T2DM treatment in 2005.[47] Prior to the advent of tirzepatide, a dual GLP-1/GIP receptor agonist, GIP was not considered therapeutically valuable.[55,60] Compared to semaglutide and dulaglutide, tirzepatide has demonstrated superior reduction in glycated hemoglobin (HbA1c) and body weight.[55] Although tirzepatide binds to the GIP receptor, its affinity for the GLP-1 receptor is approximately fivefold lower than that of endogenous GLP-1.[61]

Activation of GLP-1 and GIP receptors stimulates insulin secretion from pancreatic beta cells in response to postprandial elevation in plasma glucose, and this effect is markedly attenuated under normoglycemic conditions, thereby mitigating the risk of hypoglycemia associated with GLP-1RAs therapy.[55] Furthermore, GLP-1RAs promote beta cell proliferation and inhibit apoptosis.[58] GIP receptors are expressed on the alpha cells of islets, whereas approximately 10–15% of alpha cells express GLP-1 receptors.[62] GLP-1 receptor activation inhibits glucagon secretion, whereas GIP receptor activation increases glucagon secretion during normoglycemia or hypoglycemia, but suppresses glucagon secretion under hyperglycemic conditions.[63]

Gastric emptying significantly influences postprandial glycemic responses and represents a therapeutic target for diabetes management.[64] The glucose-lowering effects of GLP-1RAs are predominantly attributed to their modulation of gastric emptying rather than their direct pancreatic effects.[54] GLP-1 receptor activation delays gastric emptying by inhibiting gastric peristalsis and increasing pyloric sphincter tone,[65] and this effect is more pronounced in individuals exhibiting rapid baseline gastric emptying.[66] The vagus nerve mediates GLP-1's influence on gastrointestinal motility,[67] as evidenced by the absence of gastric emptying delay in patients who have undergone vagotomy.[68] GLP-1 receptors located in the gastric mucosa regulate insulin secretion but do not affect gastric motility.[69] Conversely, GLP-1 receptors in the myenteric plexus activate nitrergic and cyclic AMP signaling pathways to inhibit vagal activity within the gut,[70] resulting in decreased phasic gastric contractions, delayed gastric emptying, reduced gastric acid secretion, and increased fasting and postprandial gastric volumes.[71]

The effect of GLP-1RAs on gastric emptying varies according to the frequency and duration of exposure. Notably, GLP-1 significantly suppressed plasma pancreatic polypeptide concentrations following the first meal,[68] but this effect diminished substantially after the second test meal,[72] suggesting autonomic nervous system adaptation to continuous GLP-1 administration. Nevertheless, a significant delay in gastric emptying persisted after the second meal.[73]

In 2014, the FDA approved daily liraglutide and weekly semaglutide for pharmacological treatment in patients with a body mass index (BMI) exceeding 30 or greater than 27 in the presence of comorbidities, such as T2DM, hypertension, or obstructive sleep apnea.[74] In Australia, liraglutide is approved for weight reduction, whereas semaglutide and dulaglutide are used off-label for obesity management.[75] GLP-1 and GIP receptors expressed in the hypothalamus and brainstem nuclei regulate appetite, satiety, and energy balance.[55] GLP-1 receptors are also present in the hippocampus, neocortex, spinal cord, and cerebellum.[58] GLP-1RAs therapy has been associated with significantly greater weight loss in non-diabetic patients than in diabetic patients.[74] For instance, in the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial, weekly semaglutide administration resulted in a mean body weight reduction of 14.9% from baseline among overweight or obese non-diabetic individuals,[76] a magnitude of weight loss previously observed only following bariatric surgery. Similarly, tirzepatide, a dual GLP-1/GIP receptor agonist, achieved an average weight loss of 15% at 72 weeks in non-diabetic obese patients, with greater reductions observed at the higher 15 mg dose.[77]

The most frequently reported adverse effects of GLP-1RAs include nausea, vomiting, and diarrhea, which are dose-dependent and more prevalent with short-acting formulations than with long-acting agents. Gradual dose escalation improves gastrointestinal tolerability.[78] Acute pancreatitis is a rare but documented adverse event associated with exenatide use, as reported in the FDA Adverse Event Reporting System and observational studies.[79] Current guidelines from the American Association of Clinical Endocrinologists recommend cautious use of GLP-1RAs in T2DM patients with a history of pancreatitis[80] (See Figures 2 and 3).

Extensive Clinical Application of GLP-1RAs

GLP-1RAs for the Treatment of T2DM

GLP-1RAs are well established for the management of T2DM, and their clinical efficacy has been extensively investigated and validated. However, this article does not focus exclusively on the use of GLP-1RAs for T2DM treatment; consequently, the discussion herein will be broad rather than exhaustive.

GLP-1RAs exert glycemic control through multiple mechanisms, including the stimulation of insulin secretion under hyperglycemic conditions, suppression of glucagon secretion during hyperglycemia, deceleration of gastric emptying to mitigate postprandial glucose spikes, reduction of caloric intake, and promotion of weight loss.[71,81–83] Short-acting GLP-1RAs, such as exenatide and lixisenatide, primarily reduce nocturnal and fasting glucose levels, while maintaining their effect on gastric emptying over prolonged treatment periods. In contrast, long-acting GLP-1RAs, including liraglutide, dulaglutide, and semaglutide, demonstrated a more pronounced impact on nocturnal and fasting plasma glucose, as well as HbA1c, both when used alongside oral hypoglycemic agents and in combination with basal insulin.

A variety of GLP-1RAs agents are currently available, including exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide, semaglutide, and the dual GLP-1/GIP receptor agonist, tirzepatide. Each agent differs in pharmacokinetic

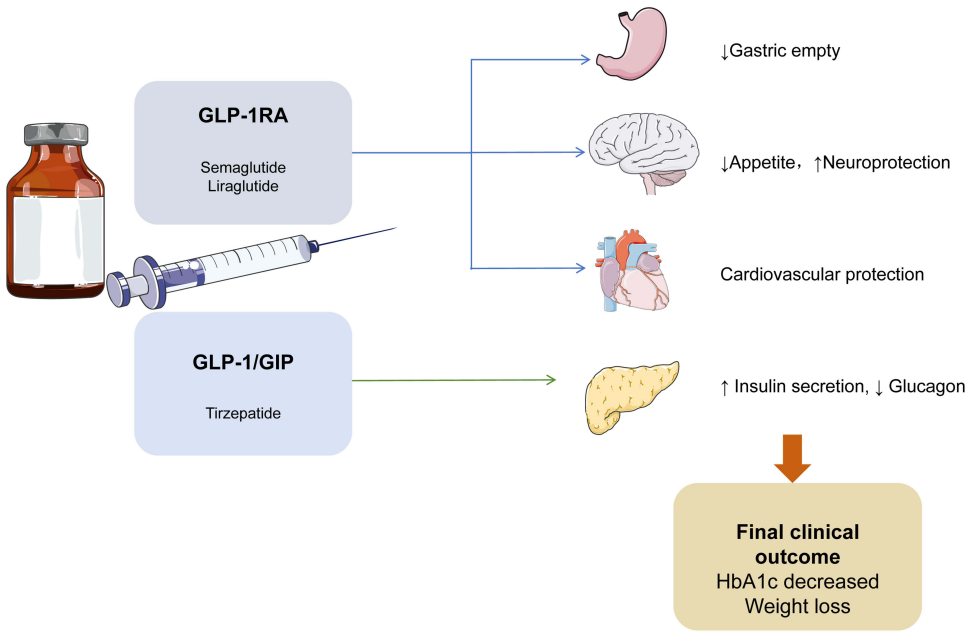

Figure 2 Mechanisms of action of GLP-1 RA and GLP-1/GIP dual agonists. ↑: improve; ↓: decrease.

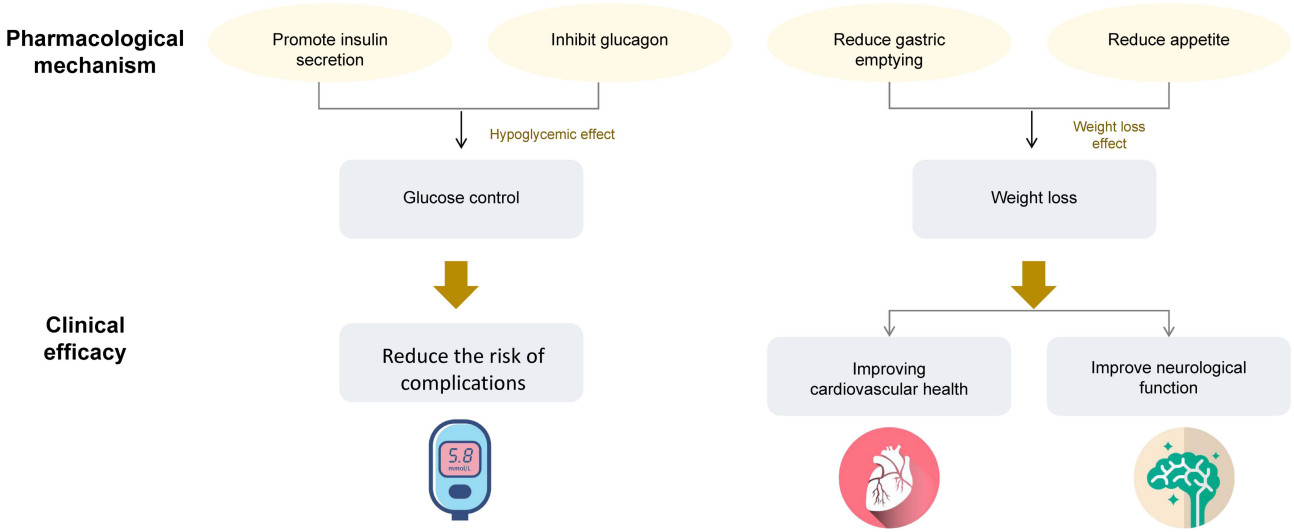

Figure 3 Mechanism Clinical Effect Comparison Causal Diagram.

properties, therapeutic efficacy, adverse event profiles, and modes of administration, necessitating individualized evaluation.[84] Clinicians must be well informed about the advantages and limitations of each GLP-1RAs to guide optimal therapeutic decision-making. Several network meta-analyses have compared the efficacy of different GLP-1RAs.[85–87] Notably, the development of GLP-1RAs therapeutics is a rapidly evolving field, with novel agents, such as orforglipron, retatrutide, and cagriSema. This underscores the urgent need for updated evidence from large-scale clinical trials.[88–90]

A recent systematic review[91] evaluated the efficacy and safety of 15 GLP-1RAs agents in adults with T2DM, encompassing 76 randomized controlled trials with 39,246 participants. The outcomes assessed included glycemic control, weight management, lipid profiles, and the incidence of adverse events. The pooled data indicated that all 15 GLP-1RAs significantly outperformed the placebo in reducing HbA1c and fasting plasma glucose levels. Among these, tirzepatide demonstrated the greatest efficacy in lowering both HbA1c and fasting glucose levels.

Currently, the development of GLP-1RAs drugs continues to be unabated, with no apparent plateau in research or innovation. Therefore, it is imperative for clinicians to remain aware of emerging evidence and advancements in this dynamic therapeutic domain (See Figures 4 and 5).

Treatment of Obesity with GLP-1RAs

GLP-1RAs enhance satiety, decrease food consumption, and delay gastric emptying, while also promoting insulin secretion and suppressing glucagon release in a glucose-dependent manner.[92,93] Subcutaneous administration of liraglutide (3 mg daily) and semaglutide (2.4 mg weekly) has been approved for obesity management. A higher subcutaneous dose of semaglutide (7.2 mg weekly)[93] is currently under investigation in a Phase III clinical trial. Despite these advances, some patients hesitate to initiate injectable therapies. Notably, semaglutide is also available in an oral formulation approved by the FDA, which incorporates an absorption enhancer[94] to facilitate uptake through the gastric mucosa. To optimize absorption, oral semaglutide must be administered early in the morning, at least 30 min prior to meals. Clinical studies indicate that in individuals with T2DM and obesity, oral semaglutide at a dose of 14 mg can improve HbA1c levels by up to 1.4% and reduce body weight by approximately 4.4 kg.[95]

A 68-week phase III trial assessed the efficacy and safety of daily oral semaglutide 50 mg combined with moderate-intensity lifestyle interventions versus placebo in a cohort of obese individuals without T2DM. The semaglutide group

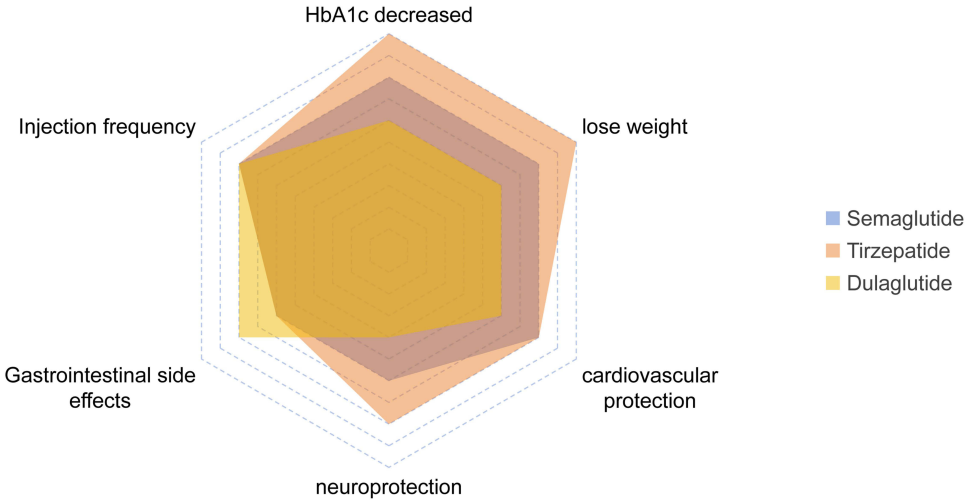

Figure 4 Comparison of radar images between GLP-1RA and tirzepatide.

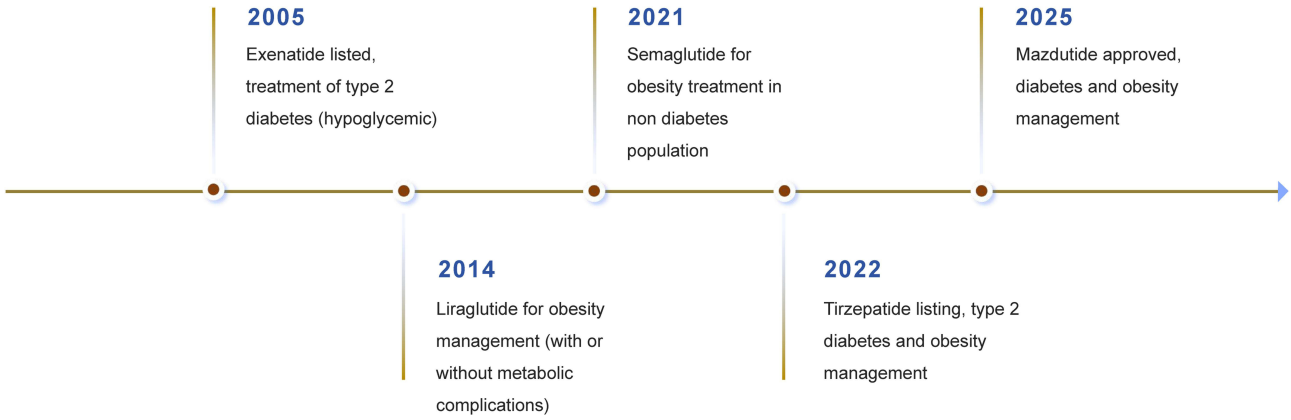

Figure 5 Indications Extension Timeline.

https://doi.org/10.2147/DDDT.S559919

experienced a mean body weight reduction of 17.4% compared to 1.8% in the placebo group, along with improvements in multiple cardiometabolic risk parameters.[96]

Orforglipron, a once-daily oral non-peptide GLP-1RAs, exhibits a distinct mode of interaction with the GLP-1 receptor compared to native GLP-1. Specifically, orforglipron functions as a potent partial agonist that preferentially activates G-protein signaling over β-arrestin recruitment to the receptor.[97] Currently under evaluation for obesity and T2DM treatment, orforglipron may offer an alternative to oral semaglutide with reduced administration constraints, as it does not require fasting prior to dosing.[98] In obese subjects, 36 weeks of orforglipron therapy produced a dose-dependent weight loss of up to 14.7%, compared to 2.3% in the placebo group, accompanied by favorable changes in cardiometabolic risk factors.[99]

Danuglipron represents another oral, non-peptide, G-protein-biased GLP-1RAs.[100] A recent Phase 2b trial in obese individuals demonstrated that 32 weeks of treatment with danuglipron at doses ranging from 40 to 200 mg twice daily resulted in an average weight loss of 11.7%, whereas the placebo group exhibited 1.4% weight gain.[101] However, treatment discontinuation rates exceeded 50% across all dosing cohorts compared to approximately 40% in the placebo group, with gastrointestinal adverse events being the most frequently reported.[101] In patients with T2DM and overweight or obesity, 16 weeks of danuglipron administered twice daily at a maximum dose of 120 mg yielded placebo-adjusted weight loss of up to 4.2 kg and a reduction in mean HbA1c levels of up to 1.2% relative to placebo in the highest dose group.[102]

Effects of GLP-1RAs on Cardiovascular System

Within the cardiovascular system, the GLP-1 receptor is expressed in both cardiac myocytes and endothelial cells,[103] indicating that GLP-1 receptor activation exerts both direct and indirect effects on cardiac and vascular functions. Evidence from a multicenter, long-term cardiovascular outcome trial demonstrated that GLP-1RAs reduce mortality associated with cardiovascular disease and confer protective effects by decreasing the incidence of myocardial infarction and nonfatal stroke.[104] GLP-1RAs have been shown to enhance endothelial cell function through anti-inflammatory and vasodilatory mechanisms. Notably, a recent STEP-HFpEF trial[105] reported that semaglutide significantly ameliorated heart failure-related symptoms in patients with obesity-related HFpEF and T2DM after one year of treatment. Furthermore, GLP-1RAs exhibit antiproliferative effects on vascular smooth muscle cells and anti-inflammatory actions on macrophages, contributing to the prevention of atherosclerosis development and progression. Some investigators have proposed that GLP-1RAs improve myocardial insulin sensitivity, enhance glucose oxidation rates, reduce fatty acid oxidation, and thereby optimize myocardial energy metabolism, ultimately improving cardiac function.[106]

In a randomized controlled trial (RCT) conducted by Mikhail et al,[106] semaglutide efficacy was evaluated in 616 patients with obesity-related heart failure and T2DM. Participants were randomized to receive either semaglutide or placebo, with outcomes assessed using the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS). The study concluded that in patients with obesity-related heart failure and T2DM with preserved ejection fraction, semaglutide treatment resulted in significantly greater reductions in heart failure-related symptoms and physical limitations, as well as more pronounced weight loss at one year compared to placebo.

Similarly, Lincoff et al[59] conducted an RCT enrolling 17,604 patients aged 45 years or older with pre-existing cardiovascular disease and a BMI of 27 or higher but without a history of diabetes. Participants were randomized in a 1:1 ratio to receive once-weekly subcutaneous injections of semaglutide (2.4 mg) or a placebo. Over a mean follow-up period of 39.8 months, semaglutide demonstrated superiority over placebo in reducing the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among overweight or obese patients with established cardiovascular disease, but without diabetes.

Neuroprotective Effect of GLP-1RAs

Cognitive dysfunction is a neurodegenerative disorder that impairs multiple cognitive domains, including memory, language, executive function, and spatial orientation, with the extent of impairment correlating with disease severity.[107] This spectrum ranges from mild cognitive impairment or mild neurocognitive disorder to more severe forms of dementia, including Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia.

Epidemiological evidence suggests an elevated risk of dementia among individuals with T2DM; however, the precise pathophysiological mechanisms underlying this association remain unclear. T2DM is characterized by a chronic proinflammatory state marked by the overexpression of cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha, alongside chemokines and other proinflammatory mediators, which contribute to insulin resistance.[108] Elevated concentrations of these inflammatory cytokines have been detected in the plasma and cerebrospinal fluid of patients with AD,[109] and postmortem analyses revealed an inflammatory milieu within the AD brain,[110] implicating inflammation as a contributory factor in the pathogenesis of dementia. Similarly, in PD, early disease stages are characterized by oxidative stress and heightened proinflammatory responses that exacerbate nigrostriatal degeneration,[111,112] with Proinflammatory mediators have also been identified in the substantia nigra of postmortem PD brains.[113]

Systemic inflammation plays a central role in the pathophysiology of hyperinsulinemia, insulin resistance, and T2DM. Insulin receptors are abundantly expressed in the central nervous system, particularly in the hippocampus and hypothalamus.[114] The concept of "cerebral insulin resistance" has emerged as a shared pathophysiological feature that links dementia and diabetes. Insulin and insulin-like growth factors I and II (IGF-I and IGF-II) are critical for neuronal and glial growth, metabolic regulation, survival, gene expression, protein synthesis, neurotransmitter network modulation, and synaptic function.[115] Cerebral insulin resistance may arise from the downregulation of insulin transport across the blood-brain barrier secondary to chronic peripheral hyperinsulinemia and systemic insulin resistance[116] as well as from the loss of neuronal membrane insulin receptors induced by soluble amyloid-beta (Aβ) oligomers.[117] Impaired insulin signaling in the brain leads to increased activity of glycogen synthase kinase 3 beta, an enzyme implicated in enhanced Aβ production and tau protein hyperphosphorylation.[118] Furthermore, cerebral hyperinsulinemia is associated with diminished clearance of Aβ peptides due to the competitive inhibition of insulin-degrading enzyme, a metalloprotease responsible for degrading both insulin and Aβ, which preferentially binds insulin over Aβ under hyperinsulinemic conditions.[119]

The neuroprotective properties of GLP-1RAs have been substantiated in vivo, supported by their ability to traverse the blood-brain barrier and the presence of GLP-1 receptors within the brain. Agents, such as liraglutide and lixisenatide, have demonstrated effective central nervous system penetration, subsequently activating GLP-1 receptors and promoting neuroprotection and neuronal progenitor cell proliferation.[120] Initial investigations into the neuroprotective effects of GLP-1RAs were conducted in diabetic animal models, where subcutaneous administration of liraglutide not only ameliorated hyperglycemia and peripheral insulin resistance, but also restored impaired brain insulin signaling, resulting in reduced tau hyperphosphorylation associated with AD pathology.[121] Additionally, liraglutide enhanced learning and memory performance in diabetic mice.[122] Notably, the beneficial effects of liraglutide on tau phosphorylation were not replicated by insulin therapy, suggesting that GLP-1RAs confer neuroprotection via mechanisms distinct from insulin signaling pathways.[123]

Following promising preclinical findings, several clinical trials have been initiated to evaluate the neuroprotective efficacy of GLP-1RAs in diverse populations, including individuals with diabetes, those at risk of cognitive decline, and patients diagnosed with AD or PD.

Alzheimer's, the most prevalent form of dementia, is strongly associated with T2DM, which increases the risk of AD morbidity. GLP-1RAs and dual GLP-1/GIP receptor agonists have demonstrated therapeutic potential in animal models and clinical settings. Transgenic mouse models of AD have shown that GLP-1RAs improve cognitive function and decelerate disease progression. For instance, liraglutide significantly reduced cerebral Aβ plaque burden in APP/PS1 mice and enhanced spatial learning and memory.[124] Similarly, semaglutide reduces Aβ deposition, improves cognition, and attenuates neuroinflammation by activating AMP-activated protein kinases and inhibiting the Toll-like receptor 4/nuclear factor kappa B signaling pathway.[124] The dual GLP-1/GIP receptor agonist tirzepatide ameliorated AD pathology in diabetic rat models by improving learning and memory, modulating cerebral glucose metabolism, promoting neurotrophic factor expression, and suppressing inflammatory responses.[125] Collectively, these findings suggest that GLP-1RAs and GLP-1/GIP dual receptor agonists are promising disease-modifying agents for AD.

Observational studies and clinical trials have further supported the role of GLP-1RAs in AD management. A large retrospective cohort study revealed that T2DM patients treated with GLP-1RAs exhibited a significantly reduced risk of

developing dementia compared with those receiving other glucose-lowering therapies.[126] In a clinical trial involving cognitively intact individuals aged 45–70 years at risk for AD, liraglutide administration for 12 weeks enhanced intrinsic connectivity within the default mode network as measured by resting-state functional magnetic resonance imaging, although no significant cognitive improvements were observed during the study period.[127] In patients with mild cognitive impairment and AD, an 18-month course of exenatide was well tolerated but did not yield significant changes in clinical or cognitive outcomes or in most neuroimaging or biomarker assessments, except for a reduction in plasma neuronal extracellular vesicle Aβ42 levels, potentially reflecting systemic neuronal status.

Parkinson's disease, characterized by dopaminergic neuronal loss in the substantia nigra leading to motor and non-motor symptoms, has also been linked to insulin resistance and impaired cerebral insulin signaling.[128] GLP-1RAs and GLP-1/GIP dual-receptor agonists have demonstrated the capacity to enhance insulin sensitivity and exert antioxidant and anti-inflammatory effects in the brain.[129] Preclinical studies in various PD animal models indicate that GLP-1RAs such as liraglutide, semaglutide, and lixisenatide promote dopamine synthesis and elevate striatal dopamine levels, thereby conferring neuroprotection to dopaminergic neurons.[130–132] The dual agonist telpor similarly exhibits neuroprotective effects by improving energy metabolism and inhibiting inflammatory pathways in PD models.[126]

Clinical trials have assessed the efficacy and safety of GLP-1RAs in PD patients with PD. For example, Meissner et al[133] conducted a randomized controlled trial evaluating lixisenatide in patients with early stage PD receiving standard treatment. Over 12 months, lixisenatide produced a modest 3-point improvement on a 132-point motor disability scale compared with placebo, primarily due to deterioration in the placebo group. Although this difference approached but did not reach the threshold for clinical significance established in other studies,[134] the findings suggest the potential neuroprotective effects of lixisenatide, possibly mediated by increased synaptic dopamine levels, as supported by preclinical and clinical research in addictive disorders.[135,136] Further investigations are warranted to elucidate the mechanisms underlying GLP-1RAs action in PD.

Beyond AD and PD, GLP-1RAs and GLP-1/GIP dual receptor agonists exhibit neuroprotective potential across a spectrum of neurological disorders. Multiple sclerosis, an autoimmune demyelinating disease of the central nervous system, may benefit from the anti-inflammatory and neuroprotective properties of GLP-1RAs.[137] Clinical observations indicate a reduced risk of multiple sclerosis relapse among T2DM patients treated with GLP-1RAs, potentially attributable to metabolic improvements and anti-inflammatory effects.[138] Experimental autoimmune encephalomyelitis models have demonstrated that liraglutide attenuates central nervous system inflammation and demyelination.[139]

Additionally, GLP-1RAs have been shown to enhance motor function and prolong survival in amyotrophic lateral sclerosis models, reduce neuronal degeneration, improve behavioral outcomes in Huntington's disease models, and confer neuroprotection following traumatic brain injury and stroke by mitigating inflammation, reducing cerebral edema, and promoting neurological recovery.[129]

GLP-1RAs and Mental Health

Worldwide, approximately 35 million individuals suffer from substance use disorders, with an estimated 280 million affected by alcohol use disorder (AUD).[140] Tobacco use is prevalent in approximately one-quarter of the global adult population.[141] AUD is linked to elevated mortality rates due to medical complications, injuries,[142] and suicide.[143] AUD's ramifications extend beyond the afflicted individual, impacting family members[144] and society at large. Harmful alcohol consumption is estimated to contribute to over 5% of global deaths and is the leading cause of preventable mortality.[74] Additionally, approximately 5 million people worldwide are estimated to have cocaine use disorder[145] and approximately 58 million individuals use opioids, including synthetic variants.[146]

The pathophysiology of addiction has been extensively investigated, revealing drug-induced dysregulation of multiple neural circuits and neurochemical systems, including dopamine, opioid peptides, corticotropin-releasing factor, dynorphin, glutamate, and gamma-aminobutyric acid (GABA). Vulnerability factors such as genetic predisposition, initial drug exposure, and social environment also play critical roles.[147–150] Among the various theoretical frameworks explaining addiction development, the incentive sensitization theory is prominent. This theory posits that excessive "wanting"—a heightened motivational drive triggered by reward-related cues—underlies addictive behaviors, distinct from the hedonic "liking" of drugs. "Wanting" is believed to originate within the dopaminergic mesolimbic pathway, projecting from the

ventral tegmental area (VTA) to the nucleus accumbens (NAcc), whereas "liking" arises from discrete hedonic hotspots in the brain, independent of dopamine release. As addiction progresses, "wanting" increasingly dominates and becomes dissociated from "liking".[148] The "dark side" hypothesis of addiction suggests that impulsivity, compulsivity, and negative urgency emerge from stress experienced during withdrawal or the negative affective phase, potentially persisting months post-withdrawal. This process involves neural circuits modulated by neuropeptides, such as corticotropin-releasing factor.[150] Dopamine plays a central role in mediating the immediate reinforcing effects of drugs, and dysregulation of the dopaminergic system has been proposed as a predisposing factor for chronic substance use and the maintenance of addiction.[151]

Dopaminergic neurons originating in the VTA project to the NAcc, amygdala, hippocampus, and prefrontal cortex, while those from the substantia nigra project to the dorsal striatum.[152] The activation or disinhibition of VTA dopaminergic neurons is critical for the potentiation of alcohol, nicotine, and opioids.[152] Cocaine exerts its effects by inhibits dopamine reuptake by blocking dopamine transporters, thereby increasing or prolonging synaptic dopamine concentrations.[152] Other central nervous system stimulants elevate synaptic dopamine via mechanisms such as dopamine reuptake inhibition, reversal of dopamine transporter function, and promotion of dopamine release.[153]

However, the mechanisms by which GLP-1 receptor stimulation modulates dopaminergic function remain unclear. In murine models, the activation of GLP-1 receptors within the VTA has been shown to attenuate the synaptic strength of the VTA-NAcc pathway,[154] although GLP-1 receptor expression in VTA neurons is relatively sparse.[155] Rat studies indicate that GLP-1 receptor activation in the VTA can enhance dopaminergic neuronal activity via presynaptic mechanisms.[156] Despite preclinical evidence and limited clinical trials, the precise influence of GLP-1 receptor stimulation on the effects of abused drugs and alcohol remains unclear. Behavioral investigations have predominantly focused on reward and reinforcement processes, with prevailing hypotheses suggesting that GLP-1RAs reduce alcohol consumption by diminishing reward-related reinforcement. Alternative mechanisms by which GLP-1 receptor stimulation may decrease alcohol intake have yet to be thoroughly explored.

The potential of GLP-1RAs to reduce alcohol consumption in humans was first reported at a scientific conference in 2011.[141] An RCT[157] evaluated the effect of 26 weeks of once-weekly exenatide treatment on the frequency of heavy drinking days in patients diagnosed with AUD. A subset of participants underwent functional magnetic resonance imaging (fMRI) and single-photon emission computed tomography (SPECT) at baseline and post-treatment to assess neurobiological changes. Regarding GLP-1-related mechanisms influencing AUD susceptibility or progression, a genetic study comprising four human association analyses demonstrated that the GLP-1 receptor 168Ser allele correlates with increased alcohol self-administration and heightened functional magnetic resonance imaging blood-oxygen-level-dependent responses in the globus pallidus during a monetary incentive delay task. This finding suggests a more dysfunctional reward system, potentially conferring greater vulnerability to AUD.[158] Conversely, a clinical trial investigating intravenous or intragastric alcohol administration reported no significant alterations in plasma GLP-1 concentrations in healthy male volunteers.[159]

The modulatory effects of GLP-1RAs on cocaine addiction-related behaviors have also been well-documented.[160] Systemic administration of exenatide has been shown to suppresses conditioned place preference in cocaine-exposed mice. Two studies[161,162] examined the acute effects of exenatide on intravenous cocaine self-administration, which is considered the gold standard for assessing the effects of injected drugs including cocaine.

Two substantial preclinical investigations have assessed the effects of exenatide on opioid-related behaviors in rodents. The first study, conducted in male mice, found that exenatide treatment did not significantly alter morphine-conditioned place preference, intravenous self-administration of the short-acting synthetic opioid remifentanil, morphine-induced locomotor activity, or the somatic signs of morphine withdrawal.[163] Additionally, exenatide did not significantly affect the analgesic efficacy of morphine in the hot-plate test.[163] Notably, remifentanil self-administration was comparable to or increased in mice lacking central nervous system GLP-1 receptors relative to wild-type controls.[163] It is important to acknowledge that the association between GLP-1RAs and suicidal behavior has not been sufficiently studied. One second study evaluated exenatide and oxycodone in mice and reported that the systemic injection of exenatide into the NAcc shell reduced oxycodone self-administration and responses in a reinstatement paradigm.[164]

However, consistent with prior findings, exenatide did not significantly influence the analgesic effects of oxycodone, as assessed by the tail-immersion test.[164]

Recently, the Icelandic drug monitoring system reported cases of suicidal ideation and self-harm among patients treated with GLP-1RAs, prompting a review by the European Medicines Agency.[165] Currently, there is no evidence indicating that GLP-1RAs increase suicidal behavior. A meta-analysis[166] encompassing 16 studies revealed that although some disproportionality analyses suggested a higher suicide rate among GLP-1RAs users compared among other glucose-lowering agents, no causal relationship was established. Cohort studies involving individuals with diabetes and obesity have generally not demonstrated a significant increase in suicidal behavior. The potential of GLP-1RAs to induce psychiatric adverse events is biologically plausible given the widespread expression of GLP-1 receptors in the central nervous system,[167] their influence on neurocognitive function,[168] and their effects on inflammation, stress response, and energy metabolism, which theoretically could improve mood.[169] A meta-analysis[170] of 11 RCTs investigating the relationship between GLP-1RAs and mental health reported 318 and 281 psychiatric adverse events in the GLP-1RAs and control groups, respectively, with no evidence of publication bias and no significant differences between the GLP-1RAs and placebo groups. These findings align with those of pooled analyses from liraglutide phase 2/3 trials in obesity[171] and retrospective case-control studies in T2DM.[172] It should be noted, however, that patients in the latter study did not receive high-dose GLP-1RAs approved for obesity and that detecting mental health disorders in routine clinical practice remains challenging. Thus far, alternative methodologies, such as artificial intelligence-based social network analyses, have yielded only qualitative insights.[173]

Few studies have specifically examined the relationship between GLP-1RAs and depression. Early clinical trials in diabetic patients have indicated that GLP-1RAs treatment is associated with improvements in health-related quality of life and well-being compared with insulin and sulfonylureas.[174–176] A notably comparable study is the population-based cohort analysis by Gamble et al,[174] which utilized UK databases to assess the incidence of new-onset depression or self-harm among new users of GLP-1RAs and dipeptidyl peptidase-4 inhibitors relative to sulfonylureas. Employing a high-dimensional propensity score algorithm to adjust for confounders, this study found no significant increase in depression or self-harm rates among GLP-1RAs users. Despite variations in data sources, adjustment techniques, risk estimates, and comparator drugs, these findings collectively suggest that GLP-1RAs are not associated with an altered risk of depression. Similarly, a population-based cohort study using Taiwanese claims data did not demonstrate a significant increase in depression risk among GLP-1RAs users compared with non-users.[177]

Research on mental health outcomes beyond depression, including health-related quality of life and anxiety, suggests potential improvements associated with GLP-1RAs treatment.[175–177] Some clinical and preclinical studies have indicated the anxiolytic effects of GLP-1RAs. For instance, animal models have shown that GLP-1RAs administration reduces anxiety-like behaviors, potentially via neuromodulatory actions in brain regions such as the amygdala. In humans, case reports and small-scale studies have observed that weight loss in obese patients treated with GLP-1RAs coincides with amelioration of anxiety symptoms. Nonetheless, investigations into the anxiolytic properties of GLP-1RAs remain limited and further clinical trials are warranted to substantiate these preliminary findings.[128]

Impact of GLP-1RAs in Perioperative Period

During the perioperative period, concerns have been raised regarding the use of GLP-1RAs and their potential association with an increased risk of bronchopulmonary aspiration due to delayed gastric emptying and retention of the gastric contents. Currently, there is a paucity of robust evidence to guide anesthesiologists to effectively mitigate this risk. Historically, perioperative guidelines and reviews have not advocated the discontinuation of GLP-1RAs prior to surgical procedures. For instance, Hulst et al (2021)[178] recommended continuation of all GLP-1RAs therapies throughout the perioperative period. Similarly, a systematic review addressing the perioperative management of diabetic patients endorsed the maintenance of GLP-1RAs treatment on the day of surgery.[179]

In a single-center retrospective cohort study by Stark et al[180] involving patients undergoing esophagogastroduodenoscopy, most of whom had T2DM, 56% received dulaglutide, 37% liraglutide, and 5% exenatide. The incidence of gastric food retention was 6.8% in the GLP-1RAs group compared to 1.7% in the non-GLP-1RAs group; however, this difference was not statistically significant.[180] In a prospective cross-sectional study conducted by Sen et al[181] involving

124 patients scheduled for elective surgery under general anesthesia, gastric ultrasound revealed retained gastric contents in 35 of 62 patients receiving GLP-1RAs therapy versus 12 of 62 controls, despite adherence to the current fasting guidelines in both cohorts. Notably, no significant correlation was observed between the duration of GLP-1RAs discontinuation and the prevalence of retained gastric contents, although a trend toward reduced retention with longer discontinuation was noted. The study's limited sample size for each discontinuation interval rendered it underpowered to directly assess the risk of aspiration.

Several professional societies and institutions have addressed the perioperative management of GLP-1RAs therapy to emphasize the potential risk of pulmonary aspiration and propose strategies for risk mitigation. The American Society of Anesthesiologists Preoperative Fasting Task Force recently updated its guidelines[74] in light of emerging evidence. For patients receiving weekly GLP-1RAs formulations undergoing elective surgery, the Task Force recommends discontinuation of the medication one week prior to surgery. For short-acting, daily administered GLP-1RAs, cessation on the day of surgery is advised. These recommendations are based on studies utilizing plasma paracetamol concentration as a surrogate marker for gastric emptying; however, this methodology has inherent limitations.[182] Furthermore, the guidelines do not differentiate recommendations based on the indication for GLP-1RAs use (eg, diabetes versus obesity) or the specific surgical procedure.[74] In cases where patients report gastrointestinal symptoms on the day of surgery, postponement of the procedure is recommended.[74] If patients do not adhere to the discontinuation recommendations, the Task Force advises implementing comprehensive gastric protective measures or considering the preoperative assessment of gastric volume via ultrasound.

Ushakumari et al[183] have expressed reservations regarding The American Society of Anesthesiologists guidelines, highlighting the absence of evidence that discontinuing GLP-1RAs therapy for one day or one week reliably reduces the risk of gastroparesis. They advocate routine preoperative gastric ultrasonography and recommend anesthetic management strategies, including airway protection, rapid sequence intubation, and general anesthesia. They further suggested that anesthesiologists should be cognizant of the heightened risk of gastric content retention, esophageal reflux, and pulmonary aspiration, and should tailor fasting guidelines based on individual patient symptoms.

Raven et al[184] underscored the importance of considering the interactions between GLP-1RAs therapy, comorbid conditions, and concomitant medications that may also delay gastric emptying. They recommend a prolonged withdrawal period and a 24-hour serum monitoring regimen prior to any surgical intervention, irrespective of the surgical or anesthetic approach. This perspective aligns with recommendations from the American Gastroenterological Association Institute Rapid Clinical Practice Update Newsletter, which suggests that implementing a liquid diet on the day preceding sedation or surgery may represent a more acceptable alternative to discontinuing GLP-1RAs therapy[185] (See Figure 6).

Clinical Application of GLP-1/GIP Dual Receptor Agonist (Tirzepatide)

Currently, tirzepatide serves as a prototypical agent among the dual-receptor agonists of GLP-1 and GIP. The innovation underlying dual and even triple receptor agonists lies in their single-molecule architecture, which represents a significant advancement in peptide bioengineering.[11] Rather than combining two distinct molecules—one a GLP-1RAs and the other a GIP receptor agonist—researchers have engineered novel molecules by modifying the native amino acid sequence of GIP. This modification enables the molecule to bind and activate both GLP-1 and GIP receptors, thereby eliciting combined biochemical effects.[61] Tirzepatide is a 39-amino acid linear synthetic peptide conjugated to a C20 fatty acid moiety. The acylation technique with fatty acids, well established in diabetes therapeutics, extends the biological half-life of the peptide by facilitating albumin binding. The estimated half-life of tizepatide is approximately 116 h, supporting its once-weekly subcutaneous administration. Importantly, pharmacokinetic analyses have demonstrated no significant differences in tirzepatide metabolism among healthy individuals, patients with renal impairment,[186] or those with hepatic dysfunction,[187] obviating the need for dose adjustments in these populations.[61]

Phase II clinical trials first evaluated tirzepatide in T2DM patients managed with lifestyle modifications alone or in combination with metformin. These studies assessed the efficacy and safety of escalating weekly doses of tirzepatide from 5 mg to 15 mg over 12 weeks compared to placebo,[188] and over 26 weeks compared to placebo or dulaglutide, selective GLP-1RAs.[189] Subsequently, tirzepatide has been extensively investigated in the SURPASS program,

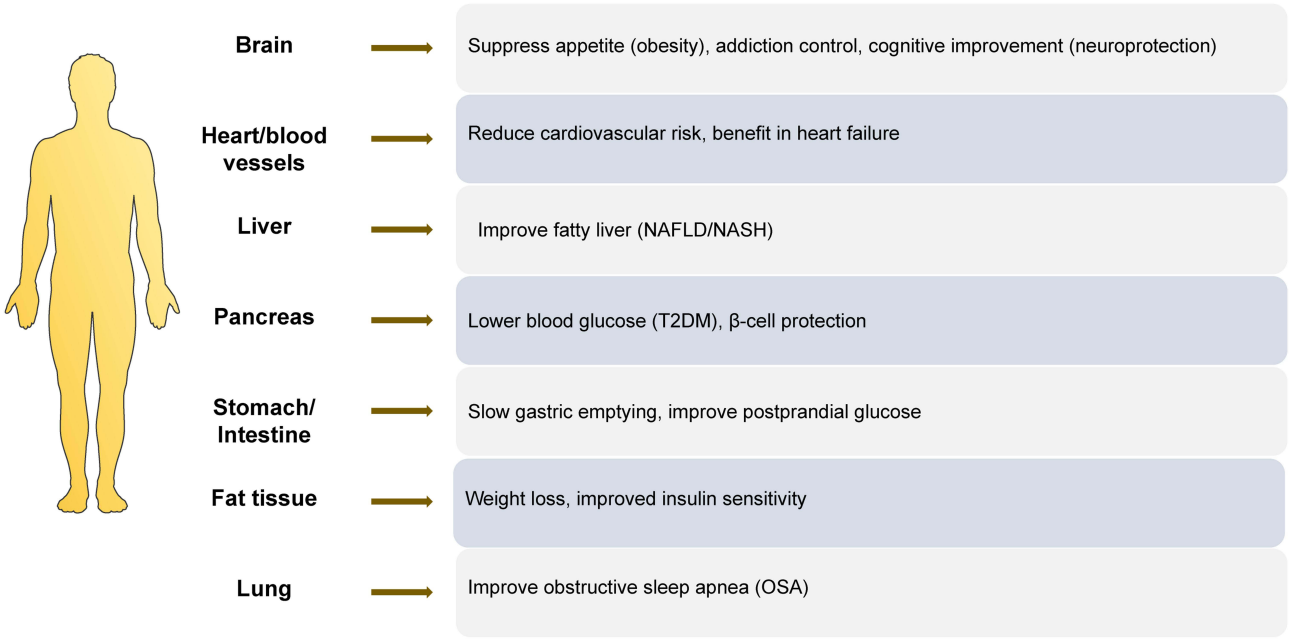

Figure 6 Multi system clinical application: intuitive display of the system and organs affected by GLP-1 drugs.

a comprehensive development initiative targeting T2DM that is inadequately controlled by various glucose-lowering regimens, including lifestyle alone (SURPASS-1),[190] metformin monotherapy (SURPASS-2),[191] metformin with or without sodium-glucose co-transporter 2 inhibitors (SGLT2i) (SURPASS-3),[192] combination therapy including metformin, SGLT2i, and sulfonylureas (SURPASS-4),[193] insulin glargine with or without metformin (SURPASS-5),[88] and insulin lispro with basal insulin (SURPASS-6).[194]

Across all SURPASS trials, tirzepatide demonstrated a dose-dependent reduction in HbA1c levels, which consistently exceeded the reductions observed with comparator treatments. A meta-analysis pooling data from two phase II and five phase III trials[195] confirmed that tirzepatide elicited greater HbA1c reductions than placebo, GLP-1RAs, and basal insulin. This translated into a significantly higher likelihood of achieving the conventional glycemic target of HbA1c <7% in tirzepatide-treated cohorts.[196] Regarding body weight, tirzepatide induced dose-dependent weight loss from baseline, as evidenced by SURPASS-2, with effects surpassing those of placebo, basal insulin, and even semaglutide, a GLP-1RAs.[191]

A noteworthy comparison between tirzepatide and semaglutide was conducted.[197] Semaglutide is recognized as the most efficacious GLP-1RAs for glycemic control, HbA1c reduction, and weight loss,[198] and has demonstrated cardiovascular benefits in the SUSTAIN-6 trial.[199] In SURPASS-2,[191] tirzepatide at doses of 10 mg and 15 mg weekly produced greater reductions in HbA1c and body weight than semaglutide administered at 1 mg weekly. Additionally, tirzepatide was associated with more pronounced decreases in blood pressure and improved lipid profiles than semaglutide.[191] An indirect comparison study[10] evaluated tirzepatide at doses of 5, 10, and 15 mg versus a higher semaglutide dose (2 mg) in T2DM patients.[200] After adjusting for baseline differences, tirzepatide at 10 mg and 15 mg demonstrated superior efficacy in lowering HbA1c and promoting weight loss relative to semaglutide at 2 mg, whereas the 5 mg tirzepatide dose showed no significant difference.

Metabolism-associated fatty liver disease represents the most prevalent chronic liver condition globally, affecting up to 75% of obese individuals. Metabolic dysfunction-associated steatohepatitis, a progressive metabolism-associated fatty liver disease subtype, is associated with an increased risk of liver fibrosis, liver-related morbidity and mortality, and cardiovascular diseases. A substudy of SURPASS-3 compared tirzepatide with insulin degludec in T2DM patients at risk of metabolism-associated fatty liver disease. After 52 weeks, tirzepatide reduced liver fat content by 30–47% from baseline, whereas insulin degludec achieved an 11% reduction.[201] Furthermore, 67–81% of tirzepatide-treated patients attained at least a 30% relative reduction in liver fat, a threshold associated with improved hepatic histology.

Obstructive sleep apnea (OSA), characterized by repeated cessation of airflow for ≥10 s during sleep accompanied by oxygen desaturation, is commonly quantified by the apnea-hypopnea index, which measures the frequency of breathing interruptions per hour. The phase III SURMOUNT-obstructive sleep apnea trial assessed the effects of tirzepatide on obstructive sleep apnea parameters.[202] After 52 weeks, tirzepatide reduced the apnea-hypopnea index by 50.7% to 58.7% from baseline and improved patient-reported sleep outcomes compared with placebo.[203]

GLP-1RAs have demonstrated sustained cardiovascular effects. However, as the use of cardioprotective agents in diabetes management increases, the incremental benefits may approach a ceiling effect. The SURPASS-CVOT trial[204] innovatively compared tirzepatide to dulaglutide, establishing non-inferiority regarding major adverse cardiovascular events and suggesting a potential 28% risk reduction compared with the extrapolated placebo. Nevertheless, the superiority of tirzepatide to dulaglutide was less pronounced than anticipated. Despite substantial improvements in glycemic control (0.8% HbA1c reduction) and weight loss (7% greater reduction), cardiovascular benefits appeared modest, raising questions regarding mechanistic saturation or trial design constraints. Exploratory analyses indicated possible mortality and renal function benefits; however, these findings warrant cautious interpretation. The trial's active-controlled/inferred-placebo design reflects evolving ethical and therapeutic standards in diabetes care. Whether GLP-1/GIP dual-receptor agonists can surpass current cardiovascular protection thresholds remains uncertain, suggesting the need for novel paradigms to overcome potential upper limits in T2DM cardiovascular risk reduction.

HFpEF accounts for over half of the heart failure cases in the United States and is increasingly prevalent among overweight and obese populations. Excessive adiposity is implicated in HFpEF pathogenesis, which is characterized by a substantial symptom burden and functional impairment. The SUMMIT study,[205] a global randomized double-blind placebo-controlled trial, evaluated the safety and efficacy of tirzepatide in adults with HFpEF and obesity. Among the 731 enrolled participants with left ventricular ejection fraction ≥50% and BMI >30, those randomized to tirzepatide experienced 36 adjudicated cardiovascular deaths or heart failure worsening events versus 56 in the placebo group, representing a 38% reduction primarily driven by fewer heart failure exacerbations. A cardiac magnetic resonance imaging substudy by SUMMIT[206] involving 175 patients assessed the effects of tirzepatide on cardiac structure and function. Of these, 106 patients completed imaging at baseline and 52 weeks, enabling the analysis of left ventricular and atrial morphology and paracardiac adipose tissue. The primary endpoint, the between-group change in left ventricular mass, demonstrated that tirzepatide significantly reduced left ventricular mass and paracardiac adipose tissue compared to placebo, with reductions in weight loss. These physiological changes may underlie the observed reduction in HFpEF events observed in the main trial. A recent analysis utilizing five US national healthcare claims cohorts from 2018 to 2024 simulated the STEP-HFpEF DM (semaglutide) and SUMMIT (tirzepatide) trials to benchmark outcomes and expanded the eligibility criteria to reflect real-world clinical practice. A head-to-head comparison revealed that both semaglutide and tirzepatide reduced the composite risk of hospitalization for HF or all-cause mortality by over 40% relative to placebo, with no significant advantage of tirzepatide over semaglutide.

Beyond the SURPASS program, the SURMOUNT trial series represents a major investigation of the efficacy of tirzepatide in obese or overweight individuals, with a focus on weight loss and diabetes risk mitigation. The phase III SURMOUNT-3 trial by Thomas et al[207] evaluated tirzepatide use following intensive lifestyle interventions. This double-blind, placebo-controlled study randomized adults with a BMI ≥30 or ≥27 plus at least one obesity-related comorbidity (excluding diabetes) who had achieved ≥5% weight loss after 12 weeks of lifestyle modification to receive tirzepatide or placebo weekly for 72 weeks. The primary endpoint (proportion achieving ≥5% additional weight loss) was met by 87.5% of the tirzepatide recipients versus 16.5% of the placebo recipients. Tirzepatide significantly augmented weight reduction beyond lifestyle intervention alone. Another SURMOUNT-3 analysis[208] demonstrated that tirzepatide improved health-related quality of life scores in obese/overweight adults, with greater benefits observed in those achieving higher weight loss thresholds and in those without baseline functional limitations.

Despite rapid advancements in GLP-1/GIP dual-receptor agonist research, several areas warrant further investigation. Notably, the SURMOUNT program excluded individuals with obesity and type 1 diabetes owing to safety concerns. Limited data from small observational and retrospective studies suggest the safety and efficacy of tirzepatide in these populations, illustrating the need for dedicated clinical trials.[209] Additionally, the potential neuroprotective effects of

tirzepatide remain unclear. Although GLP-1RAs have been extensively studied for therapeutic applications in neuropsychiatric disorders, it is yet to be determined whether tirzepatide shares similar neuroprotective properties.

Other Double Agonists and Triple Agonist

Beyond tirzepatide, pharmaceutical companies have developed additional dual receptor agonists targeting GLP-1 and glucagon (GCG) as well as triple receptor agonists.[210] Mazdutide represents the most recent advancement in GLP-1/GCG dual receptor agonists;[211–213] this agent, co-developed by Cinda Biology and Lilly Pharmaceutical, received marketing approval in China on June 27, 2025. Of particular interest are GLP-1/GCG dual-receptor agonists, especially those targeting GLP-1, GIP, and GCG receptors simultaneously.[214,215] The activation of GCG receptors is hypothesized to enhance energy expenditure, thereby facilitating weight reduction.[216] It is well established that GCG exerts hyperglycemic effects by stimulating hepatic gluconeogenesis, which may be detrimental in diabetic patients. Consequently, several therapeutic approaches have aimed to antagonize GCG activity in the management of T2DM. However, with dual or triple agonists, the hyperglycemic influence of GCG is expected to be mitigated by the hypoglycemic actions of GIP and GLP-1. Ongoing investigations are evaluating the efficacy and safety profiles of these novel receptor agonist combinations, although clinical data remain unavailable in the near future. This delay contrasts with tirzepatide, which is currently accessible in the United States and has recently obtained approval in Europe.[217]

Adverse Reactions and Safety of GLP-1RAs and GLP-1/GIP Dual Receptor Agonist

GLP-1RAs and dual agonists targeting GLP-1 and GIP receptors have demonstrated considerable efficacy in the treatment of T2DM and obesity. Nonetheless, their adverse effects and safety profiles remain critical concerns in clinical practice. Evidence indicates that GLP-1RAs confer substantial cardiovascular and renal benefits; however, their administration is frequently accompanied by adverse events, predominantly gastrointestinal.[218,219] Specifically, GLP-1RAs have been strongly linked to gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, with incidence rates influenced by dosage and concomitant therapies.[78]

Moreover, the use of GLP-1RAs may be associated with an elevated risk of pancreatitis and thyroid-related disorders, although these associations have not been definitively established.[220] Analysis of data from the US Food and Drug Administration Adverse Event Reporting System revealed that GLP-1RAs, particularly semaglutide and exenatide, are significantly correlated with gastrointestinal adverse events, including nausea, vomiting, delayed gastric emptying, and pancreatitis.[221]

Dual receptor agonists targeting GLP-1 and GIP, such as tirzepatide, have also exhibited promising efficacy in diabetes management, notably in terms of weight reduction and glycemic control. However, similar to GLP-1RAs, these agents may induce gastrointestinal adverse effects including anorexia and gastrointestinal discomfort.[222] Despite these concerns, such drugs have demonstrated beneficial effects in lowering the incidence of major cardiovascular events and strokes.[223]

Pharmacokinetically, GLP-1RAs and GLP-1/GIP dual agonists display distinct profiles attributable to their structural heterogeneity, with extended half-lives potentially correlating with an increased risk of adverse events.[224] Consequently, vigilant monitoring of patient responses is imperative during treatment, particularly when these agents are administered concomitantly with other medications, to ensure both safety and therapeutic efficacy.

The safety of GLP-1RAs and GLP-1/GIP dual agonists during pregnancy constitutes a significant area of concern, especially regarding the management of diabetes and obesity in this population. Although these agents have proven effective in regulating glycemia and body weight, their use during gestation warrants caution. Although GLP-1RAs are widely used, data concerning their safety during pregnancy, particularly with respect to fetal development, remain limited.[225] Some investigations have suggested that GLP-1RAs may indirectly influence pregnancy outcomes by ameliorating maternal metabolic status; however, their use during pregnancy is generally not recommended because of the paucity of direct clinical trial evidence.[226]

Similarly, GLP-1/GIP dual receptor agonists, such as tirzepatide, possess broad clinical efficacy, and preliminary safety evaluations have been conducted. Nonetheless, research focusing on their safety during pregnancy is scarce, with existing studies primarily addressing metabolic effects rather than gestational safety.[224] Given that GLP-1/GIP dual

agonists modulate multiple metabolic pathways, further research is necessary to elucidate their potential impact on fetal development.[227]

Additionally, safety assessments of GLP-1RAs and GLP-1/GIP dual agonists in non-pregnant women have identified common adverse reactions, including gastrointestinal discomfort and anorexia. These effects may differentially influence maternal and fetal health during pregnancy, thereby necessitating careful consideration in clinical application.[228]

In summary, despite the notable therapeutic benefits of GLP-1RAs and GLP-1/GIP dual receptor agonists in managing metabolic disorders, their safety profiles during pregnancy require a more comprehensive investigation. Clinicians should judiciously balance potential benefits against risks when considering the use of these agents in pregnant patients and, where feasible, engage in thorough preconception counseling.[225,226] Future research should prioritize the evaluation of long-term safety outcomes during pregnancy and potential fetal effects to inform safer clinical practices.

In conclusion, while GLP-1RAs and GLP-1/GIP dual agonists offer significant clinical advantages, ongoing research and vigilant monitoring of their adverse effects and safety are essential for optimizing their therapeutic application.[229,230]

Conclusion

In summary, GLP-1RAs and dual-receptor agonists targeting both GLP-1 and GIP receptors have introduced significant advancements in the management of endocrine and metabolic disorders and their associated complications, establishing themselves as central therapeutic modalities within this domain. GLP-1RAs exert their effects by activate GLP-1 receptors, thereby enhancing insulin secretion, suppressing glucagon release, delaying gastric emptying, and reducing appetite. Dual GLP-1/GIP receptor agonists, such as tirzepatide, potentiate glycemic control, weight reduction, and metabolic improvement through synergistic receptor activation. Their single-molecule design optimally integrated the incretin effects of both hormones, demonstrating superior efficacy compared to traditional GLP-1RAs.

Clinically, these agents exhibit a broad therapeutic potential. In T2DM, agents such as semaglutide and tirzepatide effectively lower HbA1c levels, blood glucose levels, and body weight, outperforming conventional oral hypoglycemic agents and insulin. In obesity management, liraglutide, semaglutide, and tirzepatide significantly reduce body mass and ameliorate cardiovascular and metabolic risk factors. The advent of oral formulations, including semaglutide and ofrutide, has further enhanced patient adherence. Cardiovascular protective effects have been observed with both drug classes, reducing major adverse cardiovascular events in patients with T2DM and obesity and demonstrating symptomatic benefits in HFpEF. Preliminary investigations into GLP-1RAs for neurodegenerative conditions, such as Alzheimer's and Parkinson's diseases, as well as addiction disorders, suggest novel therapeutic avenues; however, the neuropsychiatric efficacy of GLP-1/GIP dual agonists remains to be established. The ongoing development of novel agents, including the GLP-1/glucagon dual receptor agonist maxadutide and the exploration of triple receptor agonists, continues to expand treatment options.

Regarding safety, gastrointestinal adverse events, such as nausea, vomiting, and diarrhea, are the most common, with a higher incidence observed with short-acting formulations; gradual dose escalation can mitigate these effects. Although some studies have raised concerns about pancreatitis and thyroid-related risks, the current evidence does not conclusively establish causality. GLP-1RAs are considered safe and reduce the risk of severe hypoglycemia in patients with chronic kidney disease; nonetheless, caution is warranted perioperatively due to delayed gastric emptying and potential aspiration risk. Current guidelines recommend discontinuing GLP-1RAs one week prior to weekly dosing and on the day of surgery for daily dosing, with gastric volume assessment via ultrasound prioritized. No definitive association between GLP-1RAs and suicidal behavior has been confirmed, although long-term surveillance remains advisable. Owing to limited safety data during pregnancy, careful risk-benefit assessment and pre-pregnancy counseling are imperative.

Limitations persist in the extant literature: data on the safety and efficacy of tirzepatide in type 1 diabetes are insufficient, and its neuroprotective mechanisms are not fully elucidated; further high-quality studies are necessary to optimize perioperative management of delayed gastric emptying; and the long-term safety and efficacy of emerging multi-agonists in special populations, such as individuals with severe obesity, require validation. Future research should prioritize long-term safety assessments, efficacy evaluations in specific populations, exploration of novel indications (eg, metabolic-associated fatty liver disease and obstructive sleep apnea), and mechanistic studies to enhance the therapeutic utility of these agents in metabolic and related diseases (See Figure 7).

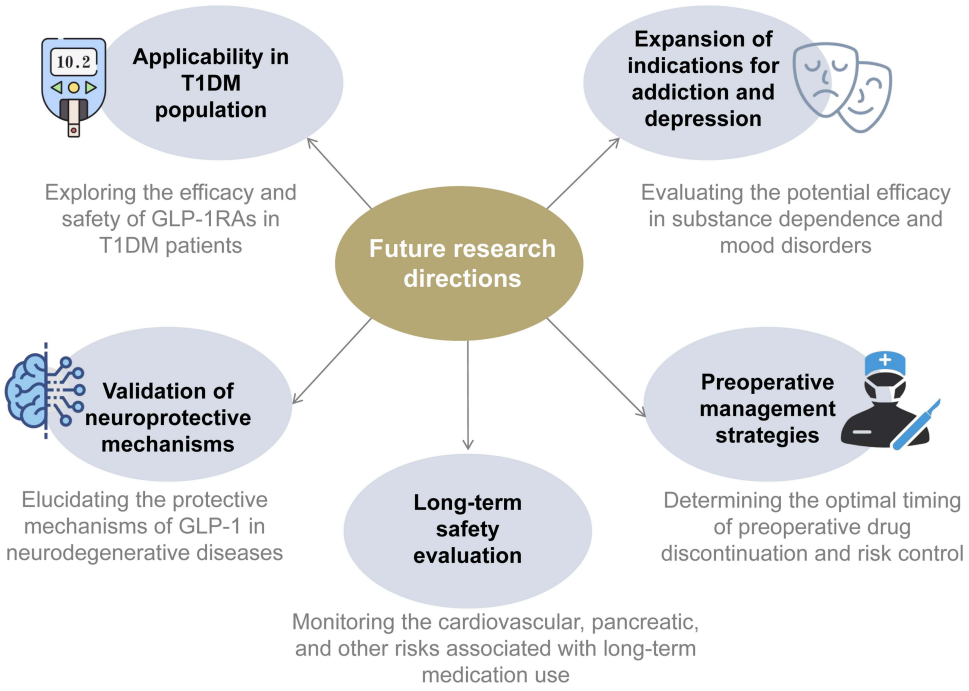

Figure 7 Future research directions.

This review provides a concise synthesis of current clinical investigations concerning GLP-1RAs and GLP-1/GIP dual receptor agonists. Given the rapid evolution of this field, future breakthroughs, including new drug approvals and expanded indications, necessitate systematic updates of the literature. Nonetheless, relative to the pace of therapeutic advancements in endocrine and metabolic diseases, such revisions are of secondary priority with greater emphasis placed on the continued clinical impact of these agents in improving patient outcomes.

Expert take-home messages:

1. Core Therapeutic Value: GLP-1RAs and GLP-1/GIP dual receptor agonists represent fundamental breakthroughs in the treatment of T2DM and obesity. Notably, tirzepatide exhibits superior glycemic and weight reduction efficacy compared with traditional GLP-1RAs, with both classes conferring cardiovascular protection.
2. Safety Management Considerations: Gastrointestinal side effects predominate, but are generally manageable via dose titration. Perioperative management requires tailored discontinuation schedules based on dosing frequency and preoperative gastric volume assessment by ultrasound. Use during pregnancy requires caution owing to insufficient safety data.
3. Directions for Future Research: Investigations should focus on confirming the efficacy of tirzepatide in type 1 diabetes, elucidating the neuroprotective potential of GLP-1/GIP dual agonists, optimizing perioperative protocols, and facilitating the clinical translation of novel multi-receptor agonists.
4. Clinical Application Guidance: Therapeutic selection should be individualized based on patient-specific factors, such as cardiovascular status, renal function, administration route preferences, and tolerability, with ongoing attention to emerging evidence to refine treatment strategies.

Despite substantial progress, critical questions remain. Future research priorities include:

- Safety in Diverse Populations: Large-scale trials are needed to establish the long-term safety and efficacy of dual receptor agonists in special populations, including patients with type 1 diabetes and pregnant women.

Mechanistic Studies in Neurodegeneration: Further elucidation of GLP-1RAs neuroprotective mechanisms (eg, anti-inflammatory effects, amelioration of cerebral insulin resistance) is warranted, along with evaluation of the neuropsychiatric potential of GLP-1/GIP dual agonists.

Long-Term Efficacy and Adherence: The impact of novel oral formulations on sustained efficacy, weight maintenance, and patient compliance requires real-world assessment and comparative analyses.

Cost-Effectiveness Analyses: Comprehensive economic evaluations are essential to support broader adoption within public health frameworks, assessing long-term benefits in cardiovascular event reduction and complication management to inform reimbursement policies.

In conclusion, GLP-1RAs and GLP-1/GIP dual receptor agonists constitute a landmark advancement in contemporary endocrine and metabolic disease therapy. Future investigations should rigorously assess their long-term safety and economic viability across diverse populations while expanding therapeutic indications, thereby maximizing the clinical benefits for millions of patients globally.

Abbreviations

GLP-1, glucagon-like peptide-1; GLP-1RAs, glucagon-like peptide-1 receptor agonists; T2DM, type 2 diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; GIP, glucose-dependent insulinotropic polypeptide; FDA, Food and Drug Administration; HbA1c, glycated hemoglobin; BMI, body mass index; RCT, randomized controlled trial; AD, Alzheimer's disease; PD, Parkinson's disease; Aβ, amyloid-beta; AUD, alcohol use disorder; VTA, ventral tegmental area; GCG, glucagon.

Funding

Special Clinical Specialty in Putuo District, Shanghai (2020tszk01, 2024tszk02), Scientific Research Project of Shanghai Municipal Health Commission (20204Y0154, 202240309), and Program of Xinglin Youqing in Putuo District (ptxlyq2302). Shanghai University of Traditional Chinese Medicine Clinical Research Backbone Training Program (2023LCRC20).

Disclosure

The authors declare that they have no affiliation with, or involvement in, any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Shanshan Yu, Xinyan Jin and Luguang Sheng are the co-first authors of this article.

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