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(REVIEW ARTICLE)

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GLP-1 RECEPTOR AGONISTS: EXPANDING INDICATIONS FROM DIABETES AND OBESITY TO CARDIOVASCULAR AND NEURODEGENERATIVE DISEASES

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ABSTRACT

Glucagon-like peptide-1 receptor agonists have evolved from glucose-lowering agents for type 2 diabetes into therapies with broad metabolic, cardiovascular, and neuroprotective effects. This review examines the expanding therapeutic landscape of GLP-1 receptor agonists, including liraglutide, semaglutide, dulaglutide, and exenatide, as well as the dual GIP/GLP-1 receptor agonist tirzepatide. In type 2 diabetes, these agents improve glycemic control and have demonstrated cardiovascular benefits in large outcome trials such as LEADER, SUSTAIN-6, and REWIND. In obesity, higher doses of liraglutide and semaglutide produce clinically meaningful weight loss, and tirzepatide has shown unprecedented efficacy in the SURMOUNT-1 trial. Emerging evidence supports potential benefits in nonalcoholic steatohepatitis, chronic kidney disease, and neurodegenerative disorders including Parkinson's disease and Alzheimer's disease. Proposed mechanisms include weight reduction, improved insulin sensitivity, anti-inflammatory effects, and direct neuroprotection. Gastrointestinal adverse effects are common, and rare but serious events such as pancreatitis and medullary thyroid carcinoma remain concerns. This review critically evaluates the evidence through early 2023, highlights unresolved questions, and discusses future directions, including oral formulations, combination incretin-based therapies, and novel indications.

Keywords: GLP-1 Receptor Agonist; Semaglutide; Liraglutide; Tirzepatide; Obesity; Neurodegenerative Disease

1 INTRODUCTION

Glucagon-like peptide-1 is an incretin hormone secreted by intestinal L cells in response to nutrient intake. It enhances glucose-stimulated insulin secretion, suppresses glucagon release, slows gastric emptying, and promotes satiety. Native GLP-1 has a very short half-life due to rapid degradation by dipeptidyl peptidase-4. GLP-1 receptor agonists are modified peptides resistant to degradation, with pharmacokinetic profiles ranging from twice-daily to once-weekly administration.

Initially developed for type 2 diabetes, GLP-1 receptor agonists have demonstrated benefits beyond glucose control. Large cardiovascular outcome trials have shown reductions in major adverse cardiovascular events, leading to guideline recommendations for patients with established cardiovascular disease or high cardiovascular risk. In obesity, GLP-1 receptor agonists produce sustained weight loss and improve cardiometabolic risk factors. More recently, preclinical

and clinical studies have suggested potential benefits in nonalcoholic steatohepatitis, chronic kidney disease, and neurodegenerative disorders.

This review summarizes the current evidence for GLP-1 receptor agonists across these indications, focusing on literature published through early 2023. It discusses mechanisms, key clinical trials, safety considerations, and future directions.

2 HARMACOLOGY AND MECHANISMS

GLP-1 receptors are expressed in pancreatic β-cells, the gastrointestinal tract, the central nervous system, the heart, kidneys, and blood vessels. Activation stimulates insulin secretion in a glucose-dependent manner, reduces glucagon, and delays gastric emptying. In the central nervous system, GLP-1 receptor activation reduces appetite and food intake, contributing to weight loss.

Beyond metabolic effects, GLP-1 receptor agonists have anti-inflammatory and antioxidant properties. They reduce markers of systemic inflammation, improve endothelial function, and may protect against ischemia–reperfusion injury. In the brain, GLP-1 receptor agonists have been shown to reduce neuroinflammation, promote neurogenesis, and improve mitochondrial function. These actions provide a mechanistic basis for potential neuroprotective effects.

Tirzepatide is a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide receptors. It produces greater weight loss and glycemic improvement than selective GLP-1 receptor agonists, likely due to complementary effects on appetite, energy expenditure, and insulin sensitivity.

3 TYPE 2 DIABETES AND CARDIOVASCULAR OUTCOMES

3.1 Glycemic Control

GLP-1 receptor agonists improve glycemic control with a low risk of hypoglycemia when used as monotherapy or with metformin. Once-weekly semaglutide and dulaglutide have demonstrated reductions in HbA1c of approximately 1.0–1.5%. Oral semaglutide provides a non-injectable option with similar efficacy. Tirzepatide achieved HbA1c reductions exceeding 2% in some trials, surpassing selective GLP-1 receptor agonists.

3.2 Cardiovascular Outcome Trials

The LEADER trial showed that liraglutide reduced the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke by 13% compared with placebo in patients with type 2 diabetes and high cardiovascular risk. SUSTAIN-6 demonstrated a 26% reduction in major adverse cardiovascular events with semaglutide. REWIND showed a 12% reduction with dulaglutide in a population with lower baseline risk. PIONEER 6, evaluating oral semaglutide, demonstrated cardiovascular safety. These trials have established GLP-1 receptor agonists as cardioprotective agents, with particular benefit in reducing cardiovascular death and stroke.

3.3 Renal Effects

GLP-1 receptor agonists reduce albuminuria and may slow decline in estimated glomerular filtration rate. Analyses from cardiovascular outcome trials suggest reduced risk of new or worsening nephropathy. Dedicated renal outcome trials, including FLOW with semaglutide, are ongoing, and results through early 2023 were not yet available.

4 OBESITY AND METABOLIC HEALTH

GLP-1 receptor agonists produce dose-dependent weight loss. Liraglutide 3.0 mg was approved for chronic weight management based on the SCALE trials, achieving mean weight loss of approximately 8% at one year. Semaglutide 2.4 mg, evaluated in the STEP program, produced mean weight loss of approximately 15% at 68 weeks in adults with overweight or obesity. More than one-third of participants achieved at least 20% weight loss.

Tirzepatide, a dual GIP/GLP-1 receptor agonist, demonstrated even greater efficacy. In SURMOUNT-1, participants receiving tirzepatide 15 mg lost an average of 20.9% of baseline body weight. These results approach those of bariatric surgery and have generated substantial interest in incretin-based obesity pharmacotherapy.

Weight loss with GLP-1 receptor agonists is accompanied by improvements in blood pressure, lipid profiles, glycemic measures, and quality of life. Gastrointestinal adverse events are the most common side effects and may limit tolerability, but gradual dose escalation reduces severity.

5 NONALCOHOLIC STEATOHEPATITIS AND LIVER DISEASE

Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis are closely linked to obesity and insulin resistance. GLP-1 receptor agonists may improve hepatic steatosis and inflammation through weight loss and direct hepatic effects. In a phase 2 trial, subcutaneous semaglutide 0.4 mg daily improved resolution of nonalcoholic steatohepatitis without worsening fibrosis compared with placebo. However, no significant improvement in fibrosis stage was observed. Larger phase 3 trials are needed to confirm efficacy and determine effects on long-term liver outcomes.

6 NEURODEGENERATIVE DISEASES

6.1 Parkinson's Disease

Preclinical studies have shown that GLP-1 receptor agonists protect dopaminergic neurons and improve motor function in animal models of Parkinson's disease. In a randomized, double-blind, placebo-controlled trial, exenatide once weekly was associated with modest improvements in motor function over 48 weeks, with effects persisting beyond treatment in some analyses. Mechanisms may include reduced neuroinflammation, improved mitochondrial function, and increased neurotrophic factors. Larger and longer trials are needed to determine clinical significance.

6.2 Alzheimer's Disease

GLP-1 receptor agonists may reduce amyloid-β accumulation, tau phosphorylation, and neuroinflammation in preclinical models of Alzheimer's disease. Clinical evidence is emerging. A small trial of liraglutide in patients with Alzheimer's disease suggested possible preservation of cognitive function and reduced brain amyloid. Phase 3 trials of semaglutide in early Alzheimer's disease were initiated, with results expected after 2023. If positive, these could establish a novel therapeutic approach.

6.3 Mechanisms of Neuroprotection

GLP-1 receptors are expressed in several brain regions, including the hippocampus and substantia nigra. Activation promotes synaptic plasticity, reduces apoptosis, and enhances cerebral glucose metabolism. Weight loss and improved insulin sensitivity may also contribute indirectly to cognitive benefits. The relative contributions of central versus peripheral mechanisms remain an area of active investigation.

7 SAFETY AND TOLERABILITY

Gastrointestinal adverse events, including nausea, vomiting, and diarrhea, are common and dose-dependent. Gradual dose escalation mitigates these effects. Gallbladder-related events and cholelithiasis have been reported more frequently with GLP-1 receptor agonists, particularly at higher doses for weight management. Acute pancreatitis is rare but serious. Preclinical studies in rodents showed an increased risk of medullary thyroid carcinoma, leading to contraindications in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Long-term safety data continue to be collected through registries and post-marketing surveillance.

Tirzepatide shares a similar safety profile, with gastrointestinal effects most common. Hypoglycemia is uncommon unless combined with insulin or sulfonylureas. Cardiovascular safety of tirzepatide is being evaluated in dedicated outcome trials.

8 FUTURE PERSPECTIVES

The GLP-1 receptor agonist field is advancing rapidly. Oral semaglutide has demonstrated efficacy in diabetes and is being evaluated for obesity at higher doses. Combination therapies, including GLP-1 receptor agonists with GIP, glucagon, or amylin, may further improve weight loss and metabolic outcomes. Triple agonists targeting GLP-1, GIP, and glucagon receptors are in clinical development.

Dedicated renal outcome trials will clarify the role of GLP-1 receptor agonists in chronic kidney disease. Neurodegenerative disease trials may open new indications. Personalized approaches based on genetic markers, microbiome profiles, and biomarkers of response may optimize treatment selection.

Challenges remain in ensuring equitable access, as GLP-1 receptor agonists are expensive and supply constraints have occurred. Long-term adherence is also a concern, particularly for chronic weight management. Addressing these issues will be essential to translate clinical efficacy into population-level benefit.

9 CONCLUSION

GLP-1 receptor agonists have undergone a remarkable evolution from diabetes medications to multi-system metabolic and potential neuroprotective therapies. Large cardiovascular outcome trials have established their cardioprotective benefits, while high-dose formulations and dual agonists have achieved clinically meaningful weight loss. Emerging evidence supports benefits in nonalcoholic steatohepatitis and neurodegenerative diseases, though confirmatory trials are needed. Safety concerns are generally manageable but require ongoing vigilance. With continued innovation in formulations, combinations, and indications, GLP-1 receptor agonists are poised to remain a cornerstone of metabolic and potentially neurological disease management.

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